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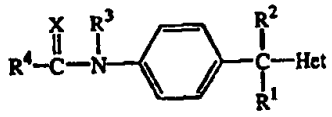

(I)

(57) Abstract

The present invention is concerned with compounds of formula (I) the *N*–oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein X represents O, S or NR^3; R^1 represents hydrogen, hydroxy, C_{1-6}alkyl or aryl; R^2 represents hydrogen; optionally substituted C_{1-12}alkyl; C_{3-7}cycloalkyl; C_{2-8}alkenyl; aryl; Het^1; or R^1 and R^2 taken together may form a bivalent radical of formula $-(CH_2)_n-$ wherein n is 2, 3, 4, 5 or 6; R^3 represents hydrogen, optionally substituted C_{1-6}alkyl, aryl, Het^1; R^4 represents hydrogen; hydroxy; mercapto; C_{1-6}alkyloxy; C_{1-6}alkylthio; aryloxy; arylthio; Het^1–oxy; Het^1–thio; optionally substituted C_{1-12}alkyl; optionally substituted C_{2-8}alkenyl; optionally substituted C_{2-8}alkynyl; optionally substituted C_{3-7}cycloalkyl; optionally substituted C_{5-7}cycloalkenyl; aryl; Het^1; or $-Alk-NR^3R^5$ (i) or $-NR^3R^5$ (ii) wherein Alk represents C_{1-6}alkanediyl; and R^5 represents hydrogen, C_{1-6}alkyl, aryl, Het^1, (aryl or Het^1)C_{1-6}alkyl, (aryl or Het^1)carbonyl or (aryl or Het^1)C_{1-6}alkyloxycarbonyl; aryl represents optionally substituted indanyl, indenyl, naphtyl, 5,6,7,8–tetrahydro–2–naphtalenyl or phenyl; Het represents an optionally substituted unsaturated heterocycle; and Het^1 represents an optionally substituted monocyclic or bicyclic heterocycle; having retinoic mimetic activity; their preparation, compositions containing them and their use as a medicine.

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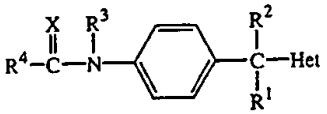
RETINOIC ACID MIMETIC ANILIDES

The present invention concerns anilides, their *N*-oxides and addition salts; it further relates to processes for their preparation, compositions comprising them. The compounds of the present invention are potent inhibitors of the retinoic acid metabolism, and hence, their use as a medicine is also described.

EP-A-0,260,744, published on March 23, 1988, discloses (1*H*-imidazol-1-ylmethyl) substituted benzimidazoles as inhibitors of the androgen formation from C_{21}-steroids, as inhibitors of the biosynthesis of thromboxane A_2, and also having the capability to increase the excretion of ureic acid. EP-A-0,371,559, published on June 6, 1990, discloses said benzimidazoles and analogous benzotriazoles as potent suppressers of the plasma elimination of endogenously or exogenously administered retinoic acid.

Retinoic acid (RA) is a key molecule in the regulation of growth and differentiation of epithelial tissues. However, RA is very rapidly metabolized by a series of enzymatic reactions, which results in its deactivation. Inhibition of RA-metabolism leads to enhanced RA levels in plasma and tissue. Therefore, compounds with such an inhibitory action, also called retinoic mimetic activity, have therapeutic and/or preventive potential in the field of dermatology and oncology.

The present invention is concerned with compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

X represents O, S or NR^3;

R^1 represents hydrogen, hydroxy, C_{1-6}alkyl or aryl;

R^2 represents hydrogen; C_{1-12}alkyl; C_{3-7}cycloalkyl; C_{2-8}alkenyl; aryl; Het^1; or C_{1-12}alkyl substituted with one or two substituents selected from C_{3-7}cycloalkyl, hydroxy, C_{1-4}alkyloxy, cyano, amino, mono- and di(C_{1-4}alkyl)amino, mono- or di(arylC_{1-4}alkyl)amino, di(arylC_{1-4}alkyl)aminocarbonyloxy, (C_{1-4}alkyl)(arylC_{1-4}alkyl)amino, mono- and di(aryl)amino, (C_{1-4}alkyl)(di(C_{1-4}alkyl)-aminoC_{1-4}alkyl)amino, pyrrolidinyl , piperidinyl, piperazinyl optionally substituted with C_{1-4}alkyl, morpholinyl, perhydro-azepinyl, carboxyl,

C_{1-4}alkyloxycarbonyl, aminocarbonyl, mono- and di(C_{1-4}alkyl)aminocarbonyl, aryl, aryloxy and arylthio; or

R^1 and R^2 taken together may form a bivalent radical of formula $-R^1-R^2-$ wherein $-R^1-R^2-$ represents $-(CH_2)_n-$ wherein n is 2, 3, 4, 5 or 6;

R^3 represents hydrogen, C_{1-6}alkyl, aryl, Het^1 or C_{1-6}alkyl substituted with aryl or Het^1;

R^4 represents hydrogen; hydroxy; mercapto; C_{1-6}alkyloxy; C_{1-6}alkylthio; aryloxy; arylthio; Het^1-oxy; Het^1-thio; C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-oxy, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxy-carbonyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, aryl, Het^1; C_{2-8}alkenyl optionally substituted with one, two or three substituents selected from halo, C_{3-7}cycloalkyl, aryl, Het^1; C_{2-8}alkynyl optionally substituted with halo, C_{3-7}cycloalkyl, aryl; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl or aryl; C_{5-7}cycloalkenyl optionally substituted with C_{1-6}alkyl or aryl; aryl; Het^1; or

$-Alk-NR^3R^5$ (i) or

$-NR^3R^5$ (ii)

wherein Alk represents C_{1-6}alkanediyl; and

R^5 represents hydrogen, C_{1-6}alkyl, aryl, Het^1, (aryl or Het^1)C_{1-6}alkyl, (aryl or Het^1)carbonyl or (aryl or Het^1)C_{1-6}alkyloxycarbonyl;

aryl represents indanyl, indenyl, naphtyl, 5,6,7,8-tetrahydro-2-naphtalenyl, phenyl; said indanyl, indenyl, naphtyl or phenyl may be substituted with one, two, three, four or five substituents each independently selected from hydroxy, halo, nitro, cyano, amino, azido, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, phenyl, phenyloxy, phenylC_{1-6}alkyloxy, pyridinylC_{1-6}alkyloxy, C_{1-6}alkyloxy, formyl, carboxyl and C_{1-6}alkylcarbonyl; or two adjacent carbon atoms on said phenyl may be substituted by a single bivalent radical having the formula C_{1-12}alkanediyl or polyhaloC_{1-12}alkanediyl;

Het represents an unsaturated heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl and pyridinyl; each of said unsaturated heterocycles may optionally be substituted with amino, mercapto, C_{1-6}alkyl, C_{1-6}alkylthio or aryl; and

Het^1 represents a monocyclic heterocycle selected from pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,3,4-triazolyl, 1,2,4-triazolyl, tetrahydrofuranyl, furanyl, thiolanyl, thienyl, dioxolanyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, piperidinyl, pyridinyl,

piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, tetrahydropyranyl, pyranyl, morpholinyl and dioxanyl; each of said monocyclic heterocycles may be optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl; or a bicyclic heterocycle selected from indolinyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, benzothienyl, 2*H*-1-benzopyranyl, 3,4-dihydro-2*H*-1-benzopyranyl, benzthiazolyl, isoquinolinyl, quinolinyl, 3,4-dihydroquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, chromanyl, 1,4-benzodioxinyl, 1,4-benzoxathianyl, benzodioxanyl and benzodioxolanyl; each of said bicyclic heterocycles may be substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{5-7}cycloalkenyl is generic to cyclopentenyl, cyclohexenyl and cycloheptenyl; C_{2-8}alkenyl defines straight and branch chained hydro-carbon radicals containing one double bond and having from 2 to 8 carbon atoms such as, for example, ethenyl, 1-propenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl, 3-heptenyl, 2-octenyl and the like; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{1-12}alkyl is meant to include C_{1-6}alkyl and the higher homologues thereof having from 7 to 12 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, 2-methylhexyl, 3-ethyloctyl and the like; C_{1-12}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 12 carbon atoms such as, for example, 1,1-methanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl, 1,11-undecanediyl, 1,12-dodecanediyl, 1,1,4,4-tetramethylbutane-1,4-diyl and the like; polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl, in particular C_{1-6}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC_{1-12}alkanediyl is defined as polyhalo-substituted C_{1-12}alkanediyl, in particular C_{1-12}alkanediyl substituted with 1 to 12 halogen atoms; triazolyl is meant to include 1,2,4-triazolyl and 1,3,4-triazolyl;

tetrazolyl is meant to include 1*H*-tetrazolyl and 2*H*-tetrazolyl; benzodioxanyl is meant to include 2,3-dihydro-1,4-benzodioxinyl.

The unsaturated heteroaryl group represented by Het may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heteroaryl group is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic base and acid addition salt forms which the compounds of formula (I) are able to form. The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, hydrohalic acid, e.g. hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like acids; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic base, *i.e.* metal or amine, addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the

so-called *N*-oxide.

The term "stereochemically isomeric forms" as used hereinbefore and hereinafter defines all the possible stereoisomeric forms in which the compounds of formula (I) exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture, and in particular the racemic mixture, of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Stereochemically isomeric forms of the compounds of formula (I) and mixtures of such forms are obviously intended to be encompassed by formula (I).

In particular, some of the compounds of formula (I) and some of the intermediates hereinafter have at least one stereogenic center in their structure. This stereogenic center may be present in a R and a S configuration, said R and S notation is used in correspondance with the rules described in Pure Appl. Chem., 1976, *45*, 11-30.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. In particular, compounds of formula (I) wherein R^3 is hydrogen may exist in their corresponding tautomeric form.

Whenever used hereinafter, the term compounds of formula (I) is meant to include also the *N*-oxides, the pharmaceutically acceptable addition salts and all stereoisomeric forms.

Whenever used hereinafter, R^1 to R^4 and Het are defined as under formula (I) unless otherwise indicated.

A special group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

(a) X represents O, S, NH or N(aryl); more in particular X is O or S;

(b) R^1 represents hydrogen, hydroxy or C_{1-6}alkyl;

(c) R^2 represents hydrogen; C_{1-12}alkyl; C_{3-7}cycloalkyl; C_{2-8}alkenyl; aryl; Het^1; or C_{1-12}alkyl substituted with one or two substituents selected from hydroxy, C_{1-4}alkyloxy, cyano, mono- and di(C_{1-4}alkyl)amino, mono- or di(arylC_{1-4}alkyl)-amino, di(arylC_{1-4}alkyl)aminocarbonyloxy, (C_{1-4}alkyl)(arylC_{1-4}alkyl)amino, (C_{1-4}alkyl)(di(C_{1-4}alkyl)aminoC_{1-4}alkyl)amino, piperidinyl, piperazinyl optionally substituted with C_{1-4}alkyl, morpholinyl, C_{1-4}alkyloxycarbonyl, aryl,

aryloxy and arylthio; or

R^1 and R^2 taken together may form a bivalent radical of formula $-R^1-R^2-$ wherein $-R^1-R^2-$ represents $-(CH_2)_n-$ wherein n is 2;

(d) R^3 represents hydrogen or C_{1-6}alkyl; more in particular R^3 is hydrogen;

(e) R^4 represents hydrogen; C_{1-6}alkyloxy; aryloxy; C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxycarbonyl, arylC_{1-6}alkylthio, aryl, Het^1; C_{2-8}alkenyl optionally substituted with one, two or three substituents selected from halo, C_{3-7}cycloalkyl, aryl, Het^1; C_{2-8}alkynyl optionally substituted with aryl; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl or aryl; C_{5-7}cycloalkenyl; aryl; Het^1; or

$-Alk-NR^3R^5$ (i) or

$-NR^3R^5$ (ii)

wherein Alk represents C_{1-6}alkanediyl; and

R^5 represents hydrogen, C_{1-6}alkyl, aryl, Het^1, arylC_{1-6}alkyl, arylcarbonyl or arylC_{1-6}alkyloxycarbonyl.

Aryl is suitably indenyl, naphtyl, 5,6,7,8-tetrahydro-naphtalenyl, phenyl; said indenyl, naphtyl or phenyl may be substituted with one, two, three, four or five substituents each independently selected from hydroxy, halo, nitro, amino, azido, C_{1-6}alkylcarbonyl-amino, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, phenyl, C_{1-6}alkyloxy.

Het is suitably imidazolyl, triazolyl and pyridinyl; each of said unsaturated heterocycles may optionally be substituted with C_{1-6}alkyl, more in particular, Het is 1*H*-1-imidazolyl or 1,2,4-triazol-1-yl.

Het^1 is suitably pyrrolyl, furanyl, thienyl, isoxazolyl, thiazolyl, piperidinyl, pyridinyl, piperazinyl, pyrimidinyl, pyrazinyl, morpholinyl and dioxanyl; each of said monocyclic heterocycles may be optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl; or indolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, benzothienyl, 2*H*-1-benzopyranyl, 3,4-dihydro-2*H*-1-benzopyranyl, benzthiazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, 1,4-benzodioxinyl, benzodioxanyl and benzodioxolanyl; each of said bicyclic heterocycles may be substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl.

Particular compounds are those compounds of formula (I) wherein R^2 is C_{1-12}alkyl optionally substituted with mono- and di(C_{1-4}alkyl)amino, more in particular, R^2 is 3-pentyl, 2-propyl, 2-(dimethylamino)-ethyl or 2-(diethylamino)-ethyl.

Other particular compounds are those compounds of formula (I) wherein R^4 is C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxycarbonyl, arylC_{1-6}alkylthio, aryl, Het^1; aryl; Het^1; or a radical of formula (ii).

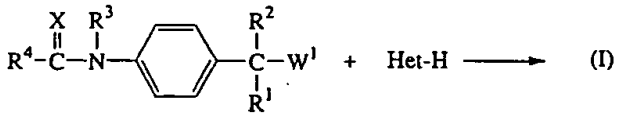
Preferred compounds are those compounds of formula (I) wherein R^3 is hydrogen; X is O and R^4 is aryl or C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxycarbonyl, arylC_{1-6}alkylthio, aryl, Het^1; or a radical of formula (ii).

Other preferred compounds are those compounds of formula (I) wherein R^3 is hydrogen, X is S and R^4 is a radical of formula (ii).

More preferred are the compounds of formula (I) wherein X is O; Het is 1,2,4-triazol-1-yl; R^1 and R^3 are hydrogen; R^2 is C_{1-6}alkyl optionally substituted with dialkylamino; and R^4 is C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxycarbonyl, arylC_{1-6}alkylthio, aryl or Het^1.

Most preferred are
4-chloro-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-α-hydroxybenzeneacetamide; the *N*-oxides, the pharmaceutically acceptable addition salts and stereoisomeric forms thereof.

In general, the compounds of formula (I) can be prepared by reacting an intermediate of formula (II) wherein W^1 is an appropriate leaving group such as, for example, a halogen, hydroxy or an alkylsulfonyloxy group, with an intermediate of formula (III) or a functional derivative thereof. For instance, a functional derivative of imidazole may be 1,1'-carbonyldiimidazole.

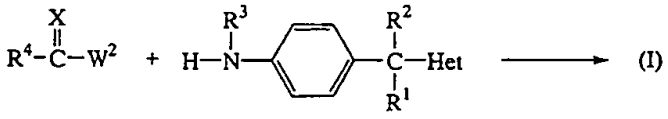


(II) (III)

Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, dichloromethane or tetrahydrofuran, in the presence of a suitable base such as, for example, potassium carbonate. In case W^1 is an hydroxy group, it may be convenient to perform the above reaction in the presence of triphenylphosphine and diethyl azodicarboxylate or a functional derivative of any of said reagents, or in the presence of 1-hydroxy-1*H*-benzotriazole and dicyclohexylcarbodiimide.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Alternatively, compounds of formula (I) may be prepared by *N*-alkylation of an intermediate of formula (IV) with an intermediate of formula (V) wherein W^2 is an appropriate leaving group such as, for example, hydroxy, a phenoxy group or a halogen, in a reaction-inert solvent such as , for example, water, *N*,*N*-dimethylformamide, dichloromethane, 1,2-dichloroethane, chloroform, *N*,*N*-dimethylacetamide, 2-propanone, benzene or the like, and optionally in the presence of a suitable base such as, for example, triethylamine, pyridine or sodiumcarbonate.

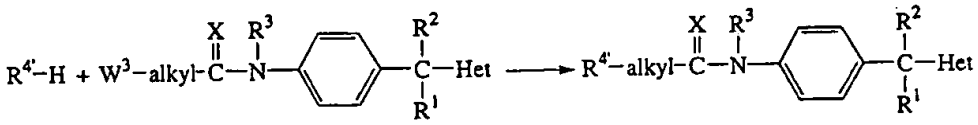


(V) (IV)

Also functional derivatives of intermediates of formula (V) may be used such as, for example, an anhydride, e.g. glutaric anhydride, dihydro-2*H*-pyran-2,6(3*H*)-dione, acetic acid anhydride; a cyanate; a thiocyanate; an isocyanate or an isothiocyanate. In some instances, it may be convenient to add an acid to the reaction medium such as, for instance, acetic acid may be used together with a cyanate.

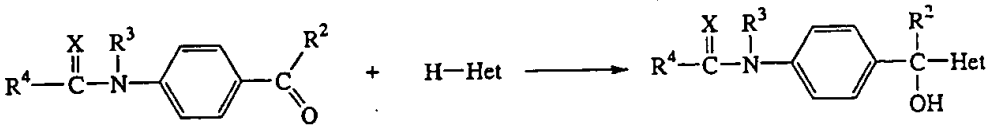
Compounds of formula (I) wherein R^4 is a Het^1C_{1-12}alkyl or a radical of formula (i), said R^4 being represented by $R^{4'}$ and said compounds being represented by formula (I-a), can be prepared by reacting an intermediate of formula (VI) wherein W^3 is a

suitable leaving group such as, for example, a halogen, with an intermediate of formula $R^{4'}$-H (VII) in a reaction-inert solvent such as, for example, acetonitrile, and in the presence of an appropriate base such as, for example, potassium carbonate.



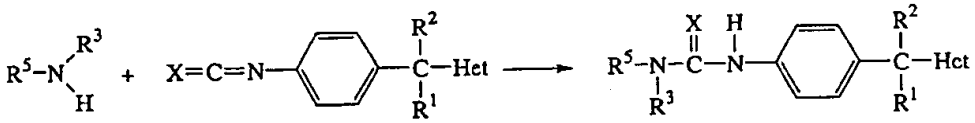
(VII) (VI) (I-a)

Compounds of formula (I) wherein R^1 is hydroxy, said compounds being represented by formula (I-b), may be prepared by reacting an intermediate of formula (VIII) with Het-H (III) or a functional derivative thereof, in the presence of an appropriate reagent such as, for example, *n*-butyllithium, in a reaction-inert solvent such as tetrahydrofuran and diethylether, and optionally in the presence of chlorotriethylsilane.



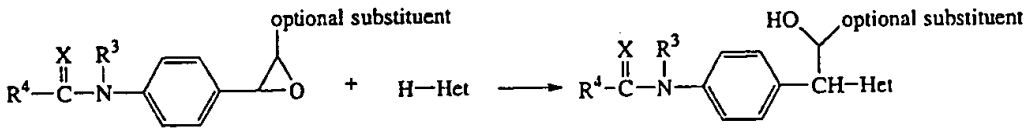
(VIII) (III) (I-b)

Compounds of formula (I) wherein R^3 is hydrogen and R^4 is attached by a nitrogen atom to the remainder of the molecule, said compounds being represented by formula (I—c), may be prepared by reacting a primary or secundary amine of formula(VIII) with an intermediate of formula (IX) in a reaction-inert solvent such as, for example, acetonitrile.



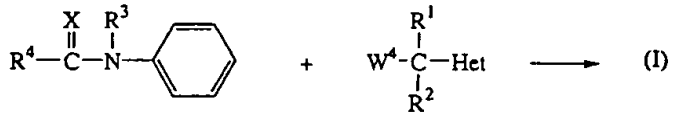
(IX) (X) (I-c)

Compounds of formula (I) wherein R^2 is optionally substituted hydroxymethyl, being represented by formula (I-d), may be prepared by reacting an intermediate of formula (XI) with Het-H (XII) or a functional derivative thereof, in a reaction-inert solvent such as, for example *N,N*-dimethylformamide.



(XI) (XII) (I-d)

Compounds of formula (I) can also be prepared by reacting an intermediate of formula (XIII) wherein W^4 is a suitable leaving group such as, for example, hydroxy, with an intermediate of formula (XIV) in an appropriate solvent such as, for example, acetic acid, and in the presence of an acid such as, for example, concentrated sulfuric acid.



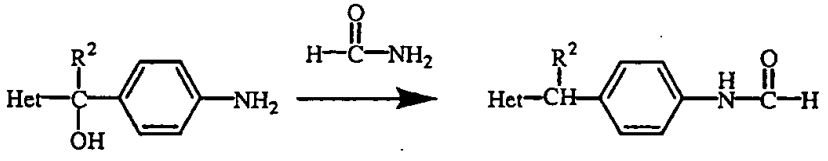
(XIV) (XIII)

Compounds of formula (I) wherein R^2 is C_{1-4}alkyloxyC_{1-12}alkyl can be prepared by reacting an intermediate corresponding to a compound of formula (I) wherein R^2 is LG-C_{1-12}alkyl wherein LG is an appropriate leaving group such as, for example, a alkylsulfonyloxy group, with $C_{1-4}alkylO^-M^+$ wherein M^+ is a suitable metal ion such as, for example Na^+, in a suitable solvent such as methanol.

Compounds of formula (I) wherein R^2 is optionally substituted C_{1-12}alkyl, said R^2 being represented by $R^{2'}$ and said compounds being represented by formula (I-e), can be prepared by reducing an intermediate of formula (XV) using a suitable reducing agent such as, for example, sodiumborohydride, in a suitable solvent such as methanol.

(XV) (I-e)

Compounds of formula (I) wherein R^1, R^3 and R^4 are hydrogen, said compounds being represented by formula (I-f), can be prepared by reacting an intermediate of formula (XXIII) with formamide in the presence of an acid such as, for example, acetic acid.



(XXIII) (I-f)

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation.

For example, compounds of formula (I) wherein R^3 is hydrogen may be converted to compounds of formula (I) wherein R^3 is other than hydrogen using art-known techniques.

Compounds of formula (I) containing an aliphatic double bond may be converted to compounds of formula (I) wherein said aliphatic double bond is reduced to a single bond using art-known hydrogenation techniques such as, for example, a reaction with hydrogen in methanol in the presence of palladium on activated charcoal as catalyst.

Compounds of formula (I) containing a carboxyl group may be esterified using art-known esterification techniques. Conversely, compounds of formula (I) containing ester may be hydrolysed to compounds of formula (I) containing the corresponding carboxyl moiety.

Also, compounds of formula (I) containing a C_{1-6}alkyloxycarbonyl substituent, may be transformed to compounds of formula (I) wherein said substituent is reduced to hydroxymethyl using for instance, lithium aluminium hydride in tetrahydrofuran; and if desired, said hydroxymethyl substituent may be further transformed to a formyl group. Said C_{1-6}alkyloxycarbonyl may also be entirely removed. Analogously, other moieties which may serve the purpose of protective group such as, for example, phenylmethyl, may also be removed using art-known techniques.

Compounds of formula (I) wherein R^1 is hydroxy can be converted to compounds of formula (I) wherein R^1 is hydrogen using a suitable reagent such as stannous chloride.

Compounds of formula (I) wherein R^4 is a phenoxy group may be converted to the ureum derivatives thereof using art-known replacement techniques. For instance, a primary or secundary amine may be used optionally in the presence of dimethylamino-pyridine and a base such as triethylamine, and 1,4-dioxane may be used as solvent.

Compounds of formula (I) wherein X is O may be converted to compounds of formula (I) wherein X is S using art-known techniques such as, for example, the use of phosphorous pentasulfide in pyridine.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise

peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

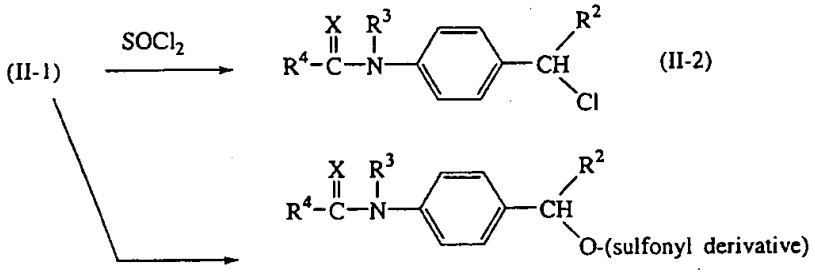
An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase such as, for example, a Chiracel AD column.

Some of the intermediates and starting materials are known compounds, may be commercially available or may be prepared according to art-known procedures.

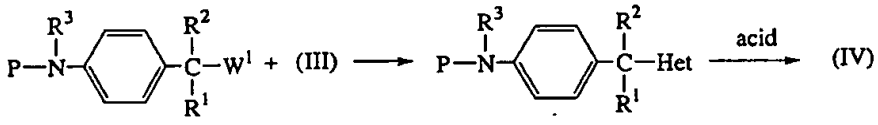
In particular, intermediates of formula (II) wherein R^1 is hydrogen and W^1 is hydroxy, said intermediates being represented by formula (II-1), may be prepared by reducing a ketone of formula (VIII). The reduction may be performed in the presence of a suitable reducing agent in an appropriate reaction-inert solvent such as, for example, sodium-borohydride in methanol or lithiumaluminiumhydride in tetrahydrofuran and water.

(VIII) (II-1)

In some instances, it may be convenient to replace the hydroxy group in intermediates of formula (II-1) by another leaving group such as, for example, a halogen or a sulfonyl derivative, e.g. a *p*-toluenesulfonyloxy group or a alkylsulfonyloxy group, thus forming intermediates of formula (II-2) or (II-3). Said reaction can be performed in a reaction-inert solvent, such as, for example, chloroform, and in the presence of a suitable reagent such as, for example, thionylchloride or methylsulfonyl chloride.



Intermediates of formula (IV) may be prepared by reacting an intermediate of formula (XVI), wherein P is a protective group such as, for example, C_{1-4}alkylcarbonyl, benzoyl or C_{1-4}alkyloxycarbonyl, with an intermediate of formula (III), and by subsequently reacting the thus formed amide derivative with an acid such as, for example, hydrochloric acid. The preparation of the intermediate amide derivative may be performed using the same procedure as the one used for the preparation of compounds of formula (I) starting from an intermediate of formula (II) and (III).

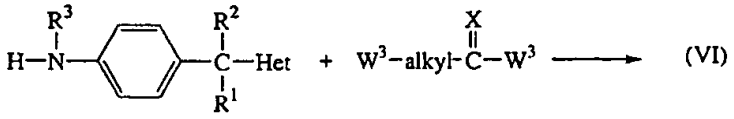


(XVI)

Intermediates of formula (IV) wherein R^3 is hydrogen, said intermediates being represented by formula (IV-1), may be prepared by reducing a nitro derivative of formula (XVII). Said reduction may be performed in the presence of a suitable reducing agent such as, for example, hydrogen, in an appropriate solvent such as, for example, methanol and in the presence of a suitable catalyst such as, for example, raney nickel.

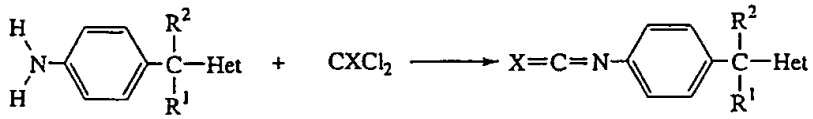
(XVII) (IV-1)

Intermediates of formula (VI) can be prepared by further reacting an intermediate of formula (IV) with an intermediate of formula (XVIII) wherein W^3 is a suitable leaving group such as, for example, a halogen, in a reaction-inert solvent such as, for example, dichloromethane, and in the presence of a base such as, for example, sodium carbonate.



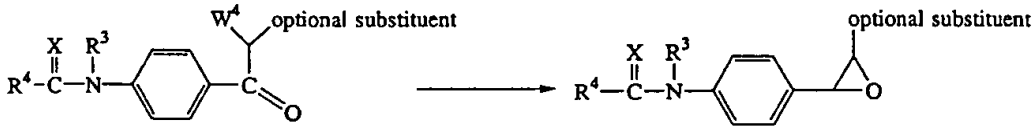
(IV) (XVIII)

Intermediates of formula (X) may be prepared by reacting an intermediate of formula (IV-1) with a reagent of formula (XIX) in a reaction inert solvent such as, for example, dichloromethane, and in the presence of a suitable base such as, for example, sodium hydroxide.



(IV-1) (XIX) (VIII)

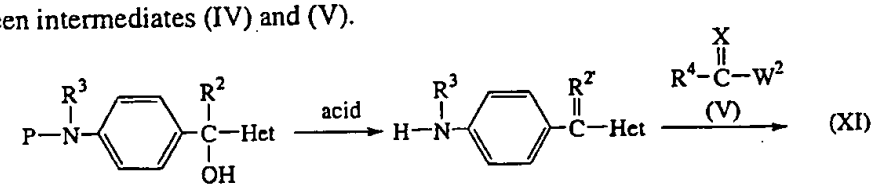
Intermediates of formula (XI) may be prepared by reductively reacting intramolecularly an intermediate of formula (XX) wherein W^4 is a suitable leaving group such as, for example, a halogen in the presence of a suitable reagent such as, for example, sodium-borohydride, in a reaction inert solvent such as, for example, methanol, and in the presence of a suitable base such as, for example, sodium hydroxide.



(XX) (XI)

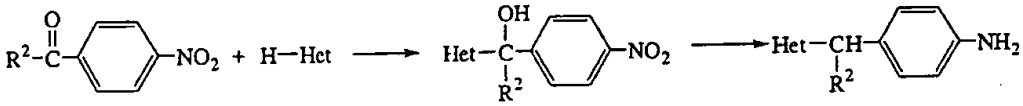
Intermediates of formula (XI) can be prepared by first dehydrating and deprotecting an intermediate of formula (XXI) wherein P is a protecting group such as, for example, C_{1-4}alkylcarbonyl, benzoyl or C_{1-4}alkyloxycarbonyl, using a suitable reagent such as, for example, an acid, e.g. hydrochloric acid, thus forming an intermediate of formula (XXII). Consequently, said intermediate of formula (XXII) may be further reacted with

an intermediate of formula (V) in the same manner as described for the reaction between intermediates (IV) and (V).



(XXI) (XXII) (XI)

Intermediates of formula (XXIII) can be prepared by first reacting an intermediate of formula (XXIV) with Het-H (III) or a functional derivative thereof, in the presence of an appropriate reagent such as, for example, *n*-butyllithium, in a reaction-inert solvent such as tetrahydrofuran and diethylether, and optionally in the presence of chlorotriethylsilane. The thus formed nitro derivative of formula (XXV) may then be reduced using for example a 15 % solution of $TiCl_3$ in water as reducing agent in a suitable solvent such as, for example, tetrahydrofuran.



(XXIV) (III) (XXIV) (XXIII)

The compounds of formula (I) suppress the plasma elimination of retinoids, such as all-*trans*-retinoic acid, 13-*cis* retinoic acid and their derivatives, resulting in more sustained plasma and tissue concentrations of retinoic acid and improved control of the differentiation and growth of various cell types. This action of the present compounds is also called retinoic mimetic activity because administering a compound of formula (I) causes the same effect as if retinoids were administered. As such, the present compounds can be used to control the rate of growth and differentiation of normal, preneoplastic and neoplastic cells, whether they are epithelial or mesenchymal; whether they are of ectodermal, endodermal or mesodermal origin.

The property to delay the metabolism of retinoic acid can be evidenced in various *in vitro* and *in vivo* experiments. A particular *in vitro* procedure is described in example C.1 and tests the inhibitory activity of the compounds of formula (I) on the metabolism of retinoic acid in human breast cancer cells. The compounds of the present invention were also effective in suppressing induced vaginal keratinization effects in ovariectomized rats as is described in example C.2.

In addition, the compounds of formula (I) show little or no endocrinological side-

effects and they have good oral availability.

In view of the above described pharmacological properties, in particular their retinoic mimetic activity, the present compounds are useful in the treatment and/or the prevention of disorders characterized by abnormal proliferation and/or abnormal differentiation of cells, in particular of cells of which the growth and differentiation is sensitive to the actions of retinoids. Such disorders are situated in the field of oncology, for example, head- and neck cancer, lung cancer, breast cancer, uterine cervix cancer, gastrointestinal tract cancer, skin cancer, bladder cancer and prostate cancer and similar disorders; and in the field of dermatology, for example, keratinization disorders such as rosacea, acne, psoriasis, severe psoriasis, lamellar ichthyosis, plantar warts, callosities, acanthosis nigricans, lichen planus, molluscum, melasma, corneal epithelial abrasion, geographic tongue, Fox-Fordyce disease, cutaneous metastatic melanoma and keloids, epidermolytic hyperkeratosis, Darier's disease, pityriasis rubra pilaris, congenital ichthyosiform erythroderma, hyperkeratosis palmaris et plantaris, melasma, hyperpigmentation and similar disorders.

Further, the compounds of formula (I) are useful in suppressing the metabolism of exogenously administered and of endogenously formed 1α,25-dihydroxy-vitamin D_3 (calcitriol). The inhibitory activity of the compounds of formula (I) on the metabolic degradation of calcitriol may be evidenced by measuring the impact of said compounds on the calcitriol degradation in human foreskin keratinocytes, pig kidney cells and human hepatoma cells. In view of their inhibitory effect on the calcitriol metabolism, the compounds of formula (I) can be used in the treatment of vitamin D deficiency states. The "classic" application of vitamin D compounds lies in the field of metabolic bone disorders. Calcitriol has also been described to influence the effects and/or production of interleukins. Further, calcitriol is of use in the treatment of diseases characterized by abnormal cell proliferation and/or differentiation, in particular, keratinization disorders such as those described hereinabove (Bouillon et al., Endocrine Reviews, 1995, *16*, 200-257).

In view of the above described uses of the compounds of formula (I), it follows that the present invention provides a method of treating warm-blooded animals suffering from diseases which are characterized by an abnormal proliferation and/or abnormal differentiation of normal, preneoplastic or neoplastic cells, whether they are epithelial or mesenchymal; whether they are of ectodermal, endodermal or mesodermal origin. Said method comprises the systemic or topical administration of a retinoic mimetic

amount of a compound of formula (I) effective in treating the above described disorders, in particular oncology disorders and keratinization disorders, optionally in the presence of an effective amount of a retinoic acid, a derivative or a stereochemically isomeric form thereof. The present invention further concerns a method of treating patients suffering from a pathological condition which may be beneficially influenced by the administration of calcitriol or a prodrug thereof, in particular oncology disorders and keratinization disorders, said method consisting of administering to a patient (a) an effective amount of calcitriol or a prodrug thereof and (b) an effective amount of a compound of formula (I).

The compounds of formula (I) may conveniently be used in combination with a chemotherapeutic agent, in particular an anti-neoplastic agent such as, e.g. daunorubicin, doxorubicin, vincristine, vinblastine, etoposide, taxol, taxotere, dactinomycin, mitoxantrone, mitomycin, trimetrexate and the like. The combination may be administered separately, simultaneously, concurrently or consecutively, or the combination may also be presented in the form of one pharmaceutical formulation. Thus, the present invention also involves a pharmaceutical product comprising (a) a compound of formula (I) and (b) a chemotherapeutic agent, as a combined preparation for simultaneous, separate or sequential use in the therapeutic or prophylactic treatment of warm-blooded animals suffering from disorders characterized by abnormal proliferation and/or abnormal differentiation of cells. Such a product may comprise a kit comprising a container containing a pharmaceutical composition of a compound of formula (I), and another container comprising a pharmaceutical composition of the chemotherapeutic agent. The product with separate compositions of the two active ingredients has the advantage that appropriate amounts of each component, and timing and sequence of administration can be selected in function of the patient. The present invention further concerns a method of treating patients suffering from disorders characterized by abnormal proliferation and/or abnormal differentiation of cells, said method consisting of administering to a patient (a) an effective amount of a compound of formula (I) and (b) an effective amount of a chemotherapeutic agent.

Thus, the present invention also relates to compounds of formula (I) as defined hereinabove for use as a medicine, in particular, for use in the manufacture of a medicament for the treatment of oncology disorders and keratinization disorders. The present invention further relates to compounds of formula (I) as defined hereinabove in combination with a retinoic acid, a derivative or a stereochemically isomeric form thereof, or in combination with calcitriol or a prodrug thereof, or in combination with a

chemotherapeutic agent, in particular an anti-neoplastic agent, for use as a medicine.

For ease of administration, the subject compounds may be formulated into various pharmaceutical forms. As appropriate compositions there may be cited all compositions usually employed for systemically or topically administering drugs. To prepare the pharmaceutical compositions of this invention, a retinoic mimetic effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g. as a transdermal patch, as a spot-on or as an ointment. Addition salts of compounds of formula (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a

semisolid such as a thickened composition which can be applied by a swab. In particular compositions, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (included scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Other such compositons are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions. Said preparations contain, besides the active ingredient, components usually employed in such preparations. Examples of such components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols, and the like. If desired, further ingredients may be incorporated in the compositions, e.g. antiinflamatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics, or other anti-acne agents.

The present invention also provides particular pharmaceutical or cosmetical compositions which comprise a pharmaceutically acceptable carrier, an effective amount of a compound of formula (I) and an effective amount of a retinoic acid, a derivative thereof or a stereochemically isomeric form thereof. Said retinoic acid containing compositions are particularly useful for treating acne or for retarding the effects of aging of the skin and generally improve the quality of the skin, particularly human facial skin.

Further, the invention also relates to particular pharmaceutical or cosmetical compositions which comprise a pharmaceutically acceptable carrier, an effective amount of a compound of formula (I) and an effective amount of calcitriol or a prodrug thereof. The latter compositions are particularly useful in treating keratinization disorders.

The invention also relates to a product containing retinoic acid or a derivative thereof and a compound of formula (I) as a combined preparation for simultaneous, separate or

sequential use in dermatological or oncological disorders. The invention also relates to a product containing calcitriol or a prodrug thereof and a compound of formula (I) as a combined preparation for simultaneous, separate or sequential use in dermatological or oncological disorders. Such products may comprise, for example, a kit comprising a container with a suitable composition containing a compound of formula (I) and another container with a composition containing calcitriol or a retinoid Such a product may have the advantage that a physician can select on the basis of the diagnosis of the patient to be treated the appropriate amounts of each component and the sequence and timing of the administration thereof.

Those of skill in the treatment of the disorders described hereinabove could determine the effective therapeutic daily amount from the test results presented in the experimental part. An effective therapeutic daily amount would be from about 0.01 mg/kg to about 40 mg/kg body weight, more preferably from about 0.1 mg/kg to about 10 mg/kg body weight. It may be appropriate to administer the therapeutically effective dose once daily or as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.1 mg to 500 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the patient may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated patient and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines. The following examples are intended to illustrate the scope of the present invention.

Experimental part

Of some compounds of formula (I) the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. Said "A" and "B" forms of those compounds of formula (I) wherein two asymmetric carbon atoms are present were separated in their pure steroechemically isomeric forms and designated as "A1" and "A2", and "B1" and "B2", without further reference to the actual stereochemical configuration.

As used hereinafter, "THF" is defined as tetrahydrofuran, "EtOAc" is defined as ethylacetate, "DIPE" is defined as diisopropyl ether and "RT" is defined as room temperature.

A) Preparation of the intermediate compounds

Example A1

Methanesulfonyl chloride (0.308 mol) was added dropwise to a solution of *N*-[4-(1-hydroxy-2-methylpropyl)phenyl]acetamide (0.1514 mol) and triethylamine (0.308 mol) in CH_2Cl_2(600ml) and the mixture was stirred at 0°C for 1 hour. The solvent was evaporated, yielding 44g (100%) of (±)-4-(acetylamino)-α-(1-methylethyl) benzenemethanol methanesulfonate(ester) (interm. 1).

Example A2

A mixture of (±)-*N*-[4-[2-methyl-1-(*1H*-1,2,4-triazol-1-yl)propyl]phenyl]acetamide (0.095 mol) in HCl (3N) (250ml) was stirred and heated at 60°C for 5 hours. The mixture was cooled, poured into ice, basified with concentrated NH_4OH and extracted with CH_2Cl_2. The organic layer was dried, filtered off and evaporated. The residue was crystallized from 2-propanone/$(C_2H_5)_2O$ and filtered off, yielding 15.5g (75%) of (±)-4-[2-methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]-benzenamine (interm. 2; mp. 117.8°C).

In a similar manner were also prepared :

(A)-4-[2-ethyl-1-(*1H*-1,2,4-triazol-1-yl)butyl]benzenamine (interm. 3);

(B)-4-[2-ethyl-1-(*1H*-1,2,4-triazol-1-yl)butyl]benzenamine (interm. 4); and

(±)-4-[2-ethyl-1-(*1H*-1,2,4-triazol-1-yl)butyl]benzenamine (interm. 5).

Example A3

1,2-Dichloroethanone (0.027 mol) was added dropwise at RT to a solution of interme diate (5) (0.0246 mol) in sodium carbonate (10%) (450ml) and CH_2Cl_2 (600ml). The mixture was stirred for 3 hours and then extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 7g (89%) of (±)-2-chloro-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]acetamide (interm. 6).

Example A4

a) (±)-4-(2-methyl-3-phenylpropyl)pyridine (0.114 mol) was added portionwise at 0°C to sulfonic acid (63ml), the mixture was stirred at 0°C for 1 hour and then at RT for 2 hours. The mixture was poured into ice, basified with NH_4OH and the precipitate was filtered off, yielding 29.31g (100%) of (±)-4-[2-methyl-1-(4-nitrophenyl)propyl]-pyridine (interm. 7).

b) Intermediate (7) (0.183 mol) in methanol (470ml), NH_4OH (47ml) and a solution of thiophene in methanol (4%; 1ml) was hydrogenated at RT with palladium on activated carbon (10%; 7.7g) as a catalyst over a 2 hour period under a 3 bar pressure in a Parr apparatus. After uptake of hydrogen, the catalyst was filtered through celite and the filtrate was evaporated, yielding 42.79g of product. A sample (3g) was taken up in CH_2Cl_2 and purified on a glass filter over silica gel (eluent : CH_2Cl_2/CH_3OH 99.5/0.5). The pure fractions were collected and evaporated. The residue was purified further by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 97.5/2.5/0.1). The pure fractions were collected and evaporated. The residue was recrystallized from $(C_2H_5)_2O$ and filtered off, yielding 0.86g of (±)-4-[2-methyl-1-(3-pyridinyl)propyl]benzenamine (interm. 8; mp. 101.5°C).

Example A5

a) A mixture of *N*-[4-(2-chloro-1-oxopropyl)phenyl]acetamide (0.19 mol), *N*-methyl-methanamine hydrochloride (1:1)(0.38 mol) and K_2CO_3 (78.8g) in CH_3CN (1400ml) was stirred and refluxed for 12 hours. The mixture was cooled, poured into water and extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent was evaporated, yielding 39.77g (89%) of (±)-*N*-[4-[2-(dimethylamino)-1-oxopropyl]phenyl]-acetamide (interm. 9).

b) Sodium tetrahydroborate (2.6 mol) was added portionwise at 0°C under N_2 flow to a mixture of intermediate (9) (2.18 mol) in methanol (5000ml). The mixture was stirred for 1 hour, poured out into ice water (5000ml) and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 357g (70%) of (±)-*N*-[4-[1-hydroxy-2-(dimethylamino)propyl]phenyl]acetamide (interm. 10).

Example A6

Sodium tetrahydroborate (0.0502 mol) was added portionwise at 0°C to a mixture of (±)-*N*-[4-(2-chloro-1-oxopropyl)phenyl]-3,4-dimethoxybenzeneacetamide (0.0502 mol) in methanol (280ml). The mixture was stirred at 0°C for 1 hour, then poured out into a mixture of NaOH (280ml) and ice, stirred for 1 hour and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 15.48g (94%) of (±)-3,4-dimethoxy-*N*-[4-(3-methyl-2-oxiranyl)phenyl]benzeneacetamide (interm. 11).

Example A7

a) n-Buthyl-lithium in hexane (1.6M; 71.6ml) was added dropwise at -70°C under N_2 flow to a mixture of 1-methylimidazole (0.1146 mol) in THF (195ml). The mixture was stirred at -70°C for 30 minutes. Chlorotrietylsilane (0.1146 mol) was added. The

mixture was brought slowly to 10°C and cooled again to -70°C. n-Buthyl-lithium in hexane (1.6M; 71.6ml) was added dropwise. The mixture was stirred at -70°C for 1 hour, brought to -15°C and cooled again to -70°C. A mixture of 4-chlorophenyl-4-nitrophenyl-methanone (0.095 mol) in THF (150ml) was added dropwise. The mixture was stirred at -70°C for 30 minutes, hydrolized and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The desired fractions were collected and their solvents were evaporated, yielding 6.5g (20%) of (±)-α-(4-chlorophenyl)-1-methyl-α-(4-nitrophenyl)-1*H*-imidazole-2-methanol (interm 12), 8.7g (26.6%) of (±)-α-(4-chlorophenyl)-1-methyl-α-(4-nitrophenyl)-1*H*-imidazole-5-methanol (interm 13) and 18g (53%) of the mixture of intermediate 12 and 13.

b) A mixture of intermediate 12 and 13 (0.09 mol) in THF (600ml) was cooled on an ice bath. $TiCl_3$ in H_2O (15%; 400ml) was added dropwise quickly. The mixture was stirred at RT for 90 minutes, poured out on ice, alkalized with NaOH 10N, then filtered over celite, pasted up and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 94/6). Two pure fractions were collected and their solvents were evaporated. Both residues were crystallized from CH_3CN and DIPE. Each phe precipitate was filtered off and dried, yielding 2g (7.1%) of (±)-α-(4-aminophenyl)-α-(4-chlorophenyl)-1-methyl-1*H*-imidazole-2-methanol (interm. 14) and 1.5g (5.3%) of (±)-α-(4-aminophenyl)-α-(4-chlorophenyl)-1-methyl-1*H*-imidazole-5-methanol (interm. 15).

B) Preparation of the compounds of formula (I)

Example B1

A mixture of (±)-4-(acetylamino)-α-(1-methylethyl)benzenemethanol methane sulfonate (ester) (0.1541 mol), 1*H*-1,2,4-triazole (0.308 mol) and K_2CO_3 (0.308 mol) in CH_3CN (500ml) was stirred and refluxed for 12 hours. The solvent was evaporated and the residue was taken up in water/CH_2Cl_2. The organic layer was dried, filtered off and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and evaporated, yielding 10g (25%) of (±)-*N*-[4-[2-methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]-phenyl]acetamide (compound 153).

Example B2

A solution of 2-methyl-3-phenyl-2-propenoyl chloride (0.0554 mol) in CH_2Cl_2 (50ml) was added dropwise to a solution of (±)-4-[2-methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]-

benzenamine (0.037 mol) in pyridine (8ml) and CH_2Cl_2 (100ml) and the mixture was stirred at RT for 4 hours. The solvent was evaporated and the residue was taken up in water/EtOAc. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.1). The pure fractions were collected and evaporated. The residue was crystallized from $(C_2H_5)_2O$/methylethylketone, yielding 2.7g (21%) of (±)-(E)-2-methyl-*N*-[4-[2-methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]phenyl]-3-phenyl-2-propenamide (compound 154).

Example B3

A mixture of 1-hydroxy-1*H*-benzotriazole (0.0227 mol) in THF (90ml) was added dropwise at 5°C under N_2 flow to a solution of (A)-4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]benzenamine (0.015 mol) and (±)-4-chloro-α-hydroxybenzeneacetic acid (0.0227 mol) in THF (95ml). A mixture of *N*,*N*-methanetetraylbis[cyclohexanamine] (0.0227 mol) in CH_2Cl_2 (37ml) was added dropwise at 5°C under N_2 flow. The mixture was stirred at RT for 15 hours. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was taken up in K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (9.25g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH 96/4). The pure fractions were collected and the solvent was evaporated, yielding 4.8g (78%) of (±)-(A)-4-chloro-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]-phenyl]-α-hydroxybenzeneacetamide (compound 16).

Example B4

(±)-(E)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-2-methyl-3-phenyl-2-propenamide (0.0144 mol) in methanol (200ml) was hydrogenated with palladium-on-charcoal 10% (0.52g) as a catalyst at RT over a 5 hour period under a 1 bar pressure in a Parr apparatus. After uptake of hydrogen, the catalyst was filtered through celite and the solvent was evaporated. The residue was crystallized from 2-butanone/DIPE, yielding 4.9g (94%)of (±)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-α-methyl-benzenepropanamide (compound 164).

Example B5

A mixture of 4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]benzenamine (0.0185 mol) in formic acid (20ml) was stirred and heated at 120°C for 15 minutes. The mixture was poured into water, basified with NaOH 3N and extracted with EtOAc. The organic layer was dried, filtered off and the solvent evaporated, yielding 3.9g (86.6%) of (±)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]formamide (compound 177).

Example B6

a) A mixture of 4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]benzenamine (0.023 mol) and dihydro-2*H*-pyran-2,6(3*H*)-dione (0.03 mol) in THF (200ml) was stirred and refluxed for 12 hours. When the reaction was complete, the solvent was evaporated, yielding 7.5g (±)-5-[[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]amino]-5-oxopentanoic acid (compound 218).

b) A mixture of (compound 218) (0.023 mol) in ethanol (200ml) and H_2SO_4 (3ml) was stirred and refluxed for 12 hours. When the reaction was complete, the solvent was evaporated, the residue was taken up in water and extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/ NH_4OH$ 97/3/0.1). The pure fractions were collected and evaporated. The residue was crystallized from 2-butanone and DIPE, yielding 1.45g (18%) of (±)-ethyl 5-[[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]amino]-5-oxopentanoate (compound 219).

Example B7

A mixture of (A)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-4-nitrobenzeneacetamide (0.0005 mol) in methanol (50ml) was hydrogenated at RT (p=2 bar) for 4 hours with Raney Nickel (0.2g) as a catalyst. After uptake of hydrogen, the catalyst was filtered off over celite, washed with CH_3OH and the solvent was evaporated. The residue (0.12g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96.5/3.5/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.035g (19%) of (A)-4-amino-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]benzeneacetamide (compound 145).

Example B8

A solution of $NaNO_2$ (0.0023 mol) in water (6ml) was added at 0°C/-5°C to a solution of (B)-4-amino-*N*-[4-[1-[(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-3-iodobenzeneacetamide (0.0021 mol) in HCl 2N (17ml). The mixture was stirred at 0°C for 15 minutes. A solution of NaN_3 (0.0023 mol) in water (6ml) was added. The mixture was stirred at 0°C for 2 hours, then neutralized with K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-butanone and DIPE. The precipitate was filtered off and dried, yielding 0.46g (44%) (B)-4-azido-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-3-iodobenzenacetamide (compound 259).

Example B9

A mixture of (±)-2-chloro-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]acetamide (0.0218 mol), 1-methylpiperazine (0.0436 mol) and K_2CO_3 (0.0436 mol) in CH_3CN (150ml) was stirred and refluxed for 4 hours. The mixture was cooled, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (8.13g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 3g (35.8%) (±)-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-4-methyl-1-piperazineacetamide (compound 15).

Example B10

Compound (16) (0.0116 mol) was separated into its enantiomers by column chromatography (eluent: hexane/2-propanol 50/50; column: CHIRACEL OD 20 μm). Two pure fractions were collected and their solvents were evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 1.77g (35%) (±)-A1-4-chloro-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-α-hydroxybenzeneacetamide (compound 17) and 1.72g (42%) (±)-(A2)-4-chloro-*N*-[4-[2-ethyl)-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-α-hydroxybenzeneacetamide (compound 18).

Example B11

HCl conc. (3.6ml) was added at RT to a mixture of (±)-1,1-dimethylethyl 4-[[[4-[2-ethyl-1-(1*H*-imidazol-1-yl)butyl]phenyl]amino]carbonyl]-1-piperidinecarboxylate (0.0032 mol) in EtOAc (30ml). The mixture was stirred at RT for 4 hours, then basified with a concentrated NaOH solution and extracted with EtOAc and then CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (1g) was converted into the hydrochloric acid salt (1:1) in 2-propanol. The precipitate was filtered off and dried, yielding 0.85g (68%) (±)-*N*-[4-[2-ethyl-1-(1*H*-imidazol-1-yl)butyl]-phenyl]-4-piperidinecarboxamide monohydrochloride (compound 57).

Example B12

A mixture of α-(4-chlorophenyl)-3-pyridinemethanol (0.364mol) and *N*-phenyl acetamide (0.364mol) in HOAc (360ml) and H_2SO_4 36N (38.6ml) was stirred and refluxed for 6 days. The solvent was evaporated, yielding 122.6g (±)-*N*-[4-[(4-chloro-phenyl)(3-pyridinyl)methyl]phenyl]acetamide (compound 673).

Example B13

Butyllithium, 1.6M in hexane (146ml) was added dropwise at -78°C under N_2 flow to a

solution of 2-bromopyridine (0.1348 mol) in THF (300ml). The mixture was stirred at -78°C for 20 minutes. A solution of *N*-(4-formylphenyl) acetamide (0.1226 mol) in THF (300ml) was added at -60°C/-70°C. The mixture was stirred at -60°C/-70°C for 1 hour, then poured out into ice water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (27g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether and 2-propanone. The precipitate was filtered off and dried, yielding 5.09g (17%) (±)-*N*-[4-[hydroxy(2-pyridinyl)methyl]phenyl]-acetamide (compound 688).

Example B14

To a solution of 4-[2-methyl-1-(3-pyridinyl)propyl]benzenamine (0.187 mol) into CH_2Cl_2 (400 ml) was added dropwise Al_2O (100 ml). The mixture was stirred for 24 hours at RT. The mixture was hydrolyzed by H_2O and neutralized by NH_4OH. The organic layer was washed with water and dried. The filtrate was evaporated, yielding 50 g of *N*-[4-[2-methyl-1-(3-pyridinyl)propyl]phenyl]acetamide (compound 671).

Example B15

1*H*-1,2,4-triazole (0.19 mol) and triphenylphosphine (0.19 mol) were added to a mixture of (±)-*N*-[4-[1-hydroxy-2-(dimethylamino)propyl]phenyl]acetamide (0.1269 mol) in THF (300ml). The mixture was cooled to 0°C. Diethyl 1,2-hydrazinedicarboxylate (0.19 mol) was added dropwise. The mixture was stirred at RT overnight. The solvent was evaporated and the residue was taken up in EtOAc and HCl 1N was added. The mixture was separated into its layers. The aqueous layer was washed with EtOAc, basified with a K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 93/7/0.1 and 80/20/0.1). Two pure fractions were collected and their solvents were evaporated. The desired fraction was recrystallized from 2-propanone/EtOAc. The precipitate was filtered off and dried, yielding 1.2g of (±)-(B)-*N*-[4-[2-(dimethylamino)-1-(1*H*-1,2,4-triazol-1-yl)propyl]phenyl]acetamide (compound 631).

Example B16

A mixture of (±)-(E)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]-2-[(4-nitrophenyl)-methylene]propanamide (0.00742 mol) in THF (80ml) and $TiCl_3$ (30ml) was stirred at 0°C for 15 minutes. The mixture was poured into water, ice and NaOH 3N and extracted with CH_2Cl_2 (2x100ml). The combined organic layers were dried, filtered and the solvent evaporated. The residue was taken up in CH_2Cl_2 and $(C_2H_5)_2O$. The

precipitate was filtered off and stirred K_2CO_3 10% and CH_2Cl_2, dried, filtered off and evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off, taken up in Na_2CO_3 10% and CH_2Cl_2. The organic layer was dried, filtered off and evaproated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The pure fractions were collected and evaporated. The residue was crystallized from $(C_2H_5)_2O$, yielding 1.5g (±)-(E)-2-[(4-aminophenyl)methylene]-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]propanamide (compound 611).

Example B17

1,1'-Carbonyldiimidazole (0.236 mol) was added at 60°C to a solution of (±)-*N*-[4-[1-hydroxy-2-methylpropyl]phenyl]acetamide (0.115 mol) in tetrahydrofuran (240ml) and the mixture was stirred at 60°C for 12 hours. The solvent was evaporated and the residue was taken up in water/CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and evaporated. The residue was crystallized from 2-propanone, yielding 28.27g (67%) (±)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]acetamide (compound 521).

Example B18

$LiAlH_4$ (0.0117 mol) was added portionwise at 0°C to a solution of (±)-ethyl (A)-β-[4-[[(3.4-dimethoxyphenyl)acetyl]amino]phenyl]-α-methyl-1*H*-imidazol-1-propanoate (0.0117 mol) in THF (78ml). The mixture was allowed to warm to RT overnight and then cooled to 0°C. $LiAlH_4$ (0.0117 mol) was added portionwise at 0°C. The mixture was allowed to warm to RT, then stirred at RT for 2 hours, poured out on ice and filtered over celite. The filtrate was extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1 and 90/10/0.2). Two pure fractions (F1 and F2) were collected and their solvents were evaporated. F1 was crystallized from 2-propanone. The precipitate was filtered off and dried, yielding 0.9g (±)-(A)-3,4-dimethoxy-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-(hydroxymethyl)propyl]phenyl]benzeneacetamide (19%) (compound 386). F2 was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.2). The pure fractions were collected and the solvent was evaporated. The residue was purified by column chromatography over amino phase (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated, yielding 0.5g (±)-(B)-3,4-dimethoxy-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-(hydroxymethyl)propyl]phenyl]-benzeneacetamide (10%) (compound 394).

Example B19

A mixture of (±)-3,4-dimethoxy-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-[methyl(phenylmethyl)-amino]propyl]phenyl]benzenacetamide (0.0066 mol) in ethanol (150ml) was hydrogenated (p=3 bar) for 90 minutes with palladium-on-charcoal 10% (3.3g) as a catalyst. After uptake of hydrogen, the catalyst was filtered off over celite, washed with CH_3OH and the solvent was evaporated. The residue (2.72g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/1). Two pure fractions were collected and their solvents were evaporated. Each residue was crystallized from 2-butanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.39g (14.5%) of (±)-(A)-3,4-dimethoxy-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-(methylamino)propyl]phenyl]benzeneacetamide (compound 400).

Example B20

A mixture of (±)-3,4-dimethoxy-*N*-[4-(3-methyl-2-oxiranyl)phenyl]benzeneacetamide (0.0442 mol) and 1*H*-imidazole (0.221 mol) in DMF (116ml) was stirred and refluxed for 6 hours. The mixture was poured out into water and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.3). The desired fraction was taken up in CH_2Cl_2, washed with a saturated NaCl solution, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 93/7/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried, yielding 1.53g (9%) of (±)-(B)-3,4-dimethoxy-*N*-[4-[2-hydroxy-1-(1*H*-imidazol-1-yl)propyl]phenyl]benzeneacetamide monohydrate (compound 402).

Example B21

A mixture of (±)-(A)-3-[4-[[(3,4-dimethoxyphenyl)acetyl]amino]phenyl]-3-(1*H*-imidazol-1-yl)-2-methylpropyl methanesulfonate (0.0011 mol) in $NaOCH_3$ (1ml) and methanol (5ml) was stirred at 80°C for 3 hours. The mixture was poured out on ice and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (0.56g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97.5/2.5/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.2g (43%) of (±)-(A)-3,4-dimethoxy-*N*-[4-[1-(1*H*-imidazol-1-yl)-3-methoxy-2-methylpropyl]phenyl]benzene-acetamide (compound 404).

Example B22

a) A mixture of compound (698) (0.0329 mol) in NaOH 3N (300ml) was stirred and refluxed for 2 hours. The mixture was cooled, poured into ice, neutralized with concentrated HCl and extracted with CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated, yielding 7.91g (88%) of (±)-4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenylthiourea (compound 699).

b) An alternative reaction procedure is the following : A solution of trifluoroacetic acid (0.0715 mol) in benzene (5ml) was added dropwise to a solution of 4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]benzenamine (0.0511 mol) and NaSCN (0.102 mol) in benzene (70ml), the mixture was stirred at RT for 1 hour and stirred further at 60°C for 24 hours. The mixture was cooled to 30°C, and extracted with CH_2Cl_2 and K_2CO_3 10%. The organic layer was washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/ NH_4OH$ 95/5/0.5 to 90/10/0.5) (35-70µm) and purified further by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/0.5) (15-40µm). The pure fractions were collected and evaporated. The residue was recrystallized from 2-propanone and $(C_2H_5)_2O$ and filtered off. The product was taken up in CH_2Cl_2, CH_3OH and norit. The product was recrystallized from 2-propanone and $(C_2H_5)_2O$ and filtered off, yielding 1.42g (±)-4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]-phenylthiourea (10%) (compound 699).

Example B23

A mixture of compound (206) (0.0104 mol), 2-pyridinamine (0.0104 mol) and *N*,*N*-dimethyl-4-pyridinamine (0.0052 mol) in 1,4-dioxane (100 ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with a 10% aqueous K_2CO_3 solution, with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone and DIPE. The precipitate was filtered off and dried, yielding 1.10 g (34.3%) (±)-*N*-(2-pyridinyl)-*N'*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]urea (compound 274).

Example B24

n-Butyllithium 1.6M in hexane (101.5ml) was added dropwise at -70°C under N_2 flow to a mixture of 1-methyl-1*H*-imidazole (0.162 mol) in THF (244ml). The mixture was stirred at -70°C for 30 minutes. Chlorotriethylsilane (0.162 mol) was added. The mixture was allowed to warm to RT. *n*-Butyllithium 1.6M in hexane (101.5ml) was

added dropwise at -70°C. The mixture was stirred at -70°C for 1 hour and brought to -15°C. A mixture of intermediate (9) (0.065 mol) in THF (152ml) was added dropwise at -70°C. The mixture was allowed to warm to RT, stirred overnight, then poured out into a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 96/4/0.5 and 80/20/2). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried, yielding 1.5g (±)-*N*-[4-[2-(dimethylamino)-1-hydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-propyl]phenyl]acetamide (compound 771).

Example B25

Benzoylchloride (0.067 mol) was added to a solution of NH_4SCN (5.09g) in 2-propanone (150ml) and the mixture was stirred and refluxed for 20 minutes. A solution of 4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]benzenamine (0.0557 mol) in 2-propanone (150ml) was added and the mixture was stirred and refluxed at 80°C overnight. The mixture was cooled, filtered through celite and the filtrate was evaporated. The residue was taken up in CH_2Cl_2. The organic layer was dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and evaporated. The residue was recrystallized from 2-propanone and DIPE, yielding (±)-*N*-benzoyl-*N'*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]thiourea (compound 698).

Example B26

A mixture of compound (689) (0.0309 mol) and iodomethane (0.062 mol) in acetonitrile (100ml) was stirred at 50°C for 2 hours. The solvent was evaporated, yielding 10.9g (91%) (±)-*N*-[4-[1-hydroxy-1-(3-pyridinium)methyl]phenyl]acetamide iodide (compound 770)

Example B27

A mixture of 1-[2-ethyl-1-(4-isothiocyanatophenyl)butyl]-1*H*-imidazole (0.0123 mol) and 2-benzothiazolamine (0.0148 mol) in acetonitrile (80ml) was stirred and refluxed for 12 hours. The solvent was evaporated and the residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 97.5/2.5/0.1). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/0.1). The pure

fractions were collected and the solvent was evaporated. The residue was crystallized from 2-butanone and DIPE. The precipitate was filtered off and dried, yielding 0.44g (9%) (±)-*N*-(2-benzothiazolyl)-*N'*-[4-[1-(1*H*-imidazol-1-yl)-2-ethylbutyl]phenyl]-thiourea (compound 705).

Example B28

A mixture of compound (651) (0.0136 mol) and phosphorous pentasulfide (0.0136 mol) in pyridine (200ml) was stirred and heated at 120°C for 12 hours. The solvent was evaporated, the residue was taken up in water, NH_4OH, CH_2Cl_2 and CH_3OH (10%), and the mixture was stirred at RT for 15 minutes. The organic layer was decanted off, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1). The desired fractions were collected and evaporated. The residue was recrystallized from 2-propanone and DIPE, filtered off and dried, yielding (22%) 1.15g 4-chloro-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]benzenethane-thioamide (compound 764).

Example B29

A solution of methyl *N'*-(3-fluorophenyl)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]-phenyl]carbamimidothioate (0.0094 mol) in NH_3/CH_3OH (60ml) was stirred and heated in autoclave at 40°C for 3 days. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 94/6/0.2 to 90.10/0.5). The pure fractions were collected and evaporated. The residue was crystallized from 2-propanone and $(C_2H_5)_2O$ and filtered off, yielding 0.89g (46%) *N'*-(3-fluorophenyl)-*N*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]guanidine (compound 744).

Example B30

A solution of KOCN (2.25g) in water was added dropwise at RT to a mixture of 4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]benzenamine (0.0278 mol) in acetic acid (4ml) and water (50ml) and the mixture was stirred at RT for 1 hour. The mixture was neutralized with NaOH 3N and extracted with CH_2Cl_2 and CH_3OH. The organic layer was washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.3). The pure fractions were collected and evaporated. The residue was recrystallized from 2-propanone, yielding 2.7g (51.4%) (±)-4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenylurea (compound 266).

Example B31

4-Fluorophenylisocyanate (0.017 mol) was added to a solution of 4-[1-(1*H*-imidazol-1-

yl)-2-methylpropyl]benzenamine (0.014 mol) in dry THF (100ml) and the mixture was stirred and refluxed for 2 hours. The mixture was cooled, the precipitate was filtered off and recrystallized from 2-propanone and CH_3OH, yielding 1.6g (32%) (±)-*N*-(4-fluorophenyl)-*N'*-[4-[1-(1*H*-imidazol-1-yl)-2-methylpropyl]phenyl]urea (compound 740).

Example B32

CH_3I (0.00814 mol) was added at RT to a mixture of compound 792 (0.00814 mol) in 2-propanone (30ml). The mixture was stirred at RT for 6 hours, poured out into H_2O and a concentrated NH_4OH solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 3.18g of methyl [4-[(2,5-dichlorophenyl)(1*H*-imidazol-1-yl)methyl]phenyl]carbamimidothioate (comp. 796).

Example B33

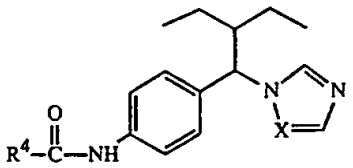
Formamide (130ml) was added to a mixture of intermediate 15 (0.043 mol) in acetic acid (130ml). The mixture was stirred at 150°C for 2 hours, cooled, poured out into ice water and basified with a concentrated NH_4OH solution. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic solution was dried, filtered and the solvent was evaporated. This fraction was crystallized from CH_2Cl_2, CH_3OH and DIPE. The precipitate was filtered off and dried, yielding 2.2g (15.1%) of (±)-*N*-[4-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-phenyl]formamide (comp. 793).

Example B34

Compound (779) (0.0132 mol) was separated into its enantiomers by column chromatography over silica gel (eluent: hexane/C_2H_5OH 80/20; column: CHIRACEL OD 20 µm). Two pure fractions were collected and their solvents were evaporated. The residue was dissolved in 2-propanone and 2-propanol and converted into the oxalic acid salt (1:1). The precipitate was filtered off and dried, yielding 2.55g of (A)-*N*-[4-[2-ethyl-1-(1*H*-imidazol-1-yl)butyl]phenyl]-3-hydroxybenzeneacetamide ethanedioate (1:1) (comp. 780) and 2.95g of (B)-*N*-[4-[2-ethyl-1-(1*H*-imidazol-1-yl)butyl]phenyl]-3-hydroxy-benzeneacetamide ethanedioate (1:1) (comp. 781).

Tables 1 to 20 list the compounds of formula (I) which were prepared analogous to one of the above examples.

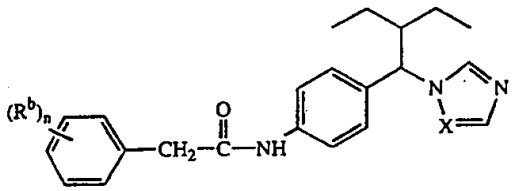
Table 1



Co. No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co. No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
1 (B1)	N; CH_3	33 (B2)	CH; 3,4-dihydro-2*H*-1-benzopyran-3-yl
2 (B2)	N; $C(CH_3)=CHC_6H_5$; (E)	34 (B2)	CH; 1,3-benzodioxolan-2-yl
3 (B2)	N; C_6H_5	35 (B2)	CH; 4-OC_2H_5-C_6H_4
4 (B3)	N; CH(OH)(4-Cl-C_6H_4)	36 (B2)	CH; (2,3-dihydro-1,4-benzodioxin-6-yl)-CH_2
5 (B2)	N; (1,3-benzodioxolan-5-yl)methyl	38 (B2)	CH; (5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphtalenyl)-CH_2
6 (B2)	N; (3,4-diOCH_3)C_6H_3	39 (B2)	CH; $(CH_2)_2$(4-OC_2H_5-C_6H_4)
7 (B2)	N; (2,3-dihydro-1,4-benzodioxin-6-yl)methyl	40 (B5)	CH; H
8 (B3)	N; $(CH_2)_3$(3,4-diOCH_3-C_6H_3)	41 (B2)	CH; CH_2-(4-C_6H_5-C_6H_4)
9 (B2)	N; OC_6H_5	42 (B2)	CH; CH_2Cl
10 (B3)	N; $(CH_2)_2$(3,4-diOCH_3-C_6H_3)	43 (B9)	CH; (1-piperidinyl)methyl
11 (B3)	N; CH(OH)(3,4-diCH_3-C_6H_3)	44 (B9)	CH; (4-CH_3-1-piperazinyl)-CH_2
12 (B2)	N; CH_2O(2-OCH_3-C_6H_4)	45 (B3)	CH; 2-methoxy-5-pyridinyl
13 (B3)	N; (2-NH_2-benzothiazol-6-yl)-CH_2	46 (B3)	CH; 1-(C_6H_5-CO)-4-piperidinyl
14 (B2)	N; CH_2Cl	47 (B9)	CH; (4-morpholinyl)-CH_2
15 (B9)	N; (4-CH_3-1-piperazinyl)-CH_2	48 (B3)	CH; $(CH_2)_3$(4-OC_2H_5-C_6H_4)
16 (B3)	N; CH(OH)(4-Cl-C_6H_4); (A)	49 (B3)	CH; CH_2O(2-OH-C_6H_4)
17(B10)	N; CH(OH)(4-Cl-C_6H_4); (A,A)	50 (B2)	CH; $CH(SCH_3)(C_6H_5)$
18(B10)	N; CH(OH)(4-Cl-C_6H_4); (A,B)	51 (B3)	CH; (2-OCH_3-5-pyridinyl)-CH_2
19 (B3)	N; CH(OH)(4-Cl-C_6H_4); (B)	52 (B3)	CH; $(CH_2)_3$(3,4-diOCH_3-C_6H_3)
20(B10)	N; CH(OH)(4-Cl-C_6H_4); (B,A)	53 (B3)	CH; 1-(*tert*-butoxy-carbonyl)-4-piperdinyl
21(B10)	N; CH(OH)(4-Cl-C_6H_4); (B,B)	54 (B3)	CH; CH(OH)(4-Cl-C_6H_4)
22 (B2)	CH; phenyl	55 (B3)	CH; $CH_2N(CH_3)_2$
23 (B2)	CH; 2,3-dihydro-1,4-benzodioxin-2-yl	56 (B3)	CH; CH(OH)(3,4-diOCH_3-C_6H_3)
24 (B3)	CH; $C(OH)(CH_3)_2$	57(B11)	CH; 4-piperidinyl
25 (B2)	CH; 1,4-benzodioxin-2-yl	58 (B3)	CH; (2-NH_2-6-benzothiazolyl)-CH_2

Co. No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co. No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
26 (B2)	CH; (2,3-dihydro-1,4-benzodioxin-2-yl)-CH_2	59 (B3)	CH; 1-methyl-4-piperidinyl
27 (B2)	CH; 2-pyrazinyl	60 (B2)	CH; OC_6H_5
28 (B2)	CH; (1,3-benzodioxolan-5-yl)-CH_2	61(B10)	CH; $(CH_2)_2(4\text{-}OC_2H_5\text{-}C_6H_4)$; (A)
29 (B2)	CH; 3,4-dihydro-2*H*-1-benzopyran-2-yl	62(B10)	CH; $(CH_2)_2(4\text{-}OC_2H_5\text{-}C_6H_4)$; (B)
30 (B2)	CH; 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphtalenyl	63(B23)	N; 2-benzothiazolyl-NH-
31 (B2)	CH; 2*H*-1-benzopyran-3-yl	64(B23)	CH; 2-benzothiazolyl-NH-
32 (B2)	CH; $(CH_2)_2(3,4\text{-}diOCH_3\text{-}C_6H_3)$	777(B3)	N; 2-benzothiazolyl
37 (B2)	CH; $CH_2O(2\text{-}OCH_3\text{-}C_6H_4)$	778(B3)	CH; 2-benzothiazolyl; oxalic acid (1:1)

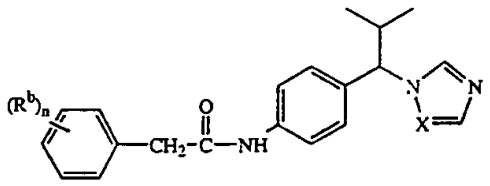
Table 2



Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt	Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
65	B2	N	$4\text{-}CH_3$	101	B2	CH	$3\text{-}OC_2H_5$; $4\text{-}OC_2H_5$
66	B2	N	4-Cl	102	B2	CH	$2\text{-}OCH_3$; $3\text{-}OCH_3$
67	B3	N	3-OH	103	B2	CH	$4\text{-}OC_6H_5$
68	B2	N	4-F	104	B2	CH	$2\text{-}CH_3$
69	B3	N	4-OH	105	B2	CH	$4\text{-}OCH_3$
70	B2	N	$3\text{-}OCH_3$	106	B2	CH	$2\text{-}CH_3$; $5\text{-}CH_3$
71	B2	N	$4\text{-}OC_2H_5$	107	B3	CH	2-OH
72	B3	N	$3\text{-}OCH_3$; 4-OH	108	B3	CH	3-OH; $4\text{-}OCH_3$
73	B2	N	$3\text{-}OCH_3$; $4\text{-}OCH_3$	109	B3	CH	3-OH; oxalic acid (1:1)
74	B2	N	3-Cl; $4\text{-}OCH_3$	110	B2	CH	3-O CH_3; $4\text{-}CH_3$
75	B2	N	3-Cl; $4\text{-}OC_2H_5$	111	B3	CH	4-OH
76	B2	N	$3\text{-}CH_3$; $4\text{-}OC_2H_5$	112	B2	CH	$3\text{-}CH_3$; $4\text{-}CH_3$
77	B2	N	$3\text{-}CH_3$; $4\text{-}CH_3$	113	B2	CH	$2\text{-}OCH_3$; 4-Cl
78	B3	N	$3\text{-}CH_3$; $4\text{-}OCH_3$	114	B2	CH	$2\text{-}OCH_3$; $6\text{-}OCH_3$
79	B3	N	3-Cl; 4-OH	115	B2	CH	$2\text{-}OCH_2C_6H_5$; $3\text{-}OCH_3$

Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
80	B2	N	3-OCH_3; 4-OCH_3; 5-OCH_3
81	B2	N	3-CH_3; 4-CH_3; 5-CH_3
82	B3	N	3-OC_2H_5; 4-OC_2H_5
83	B3	N	3-OCH_3; 4-Cl
84	B3	N	3-OCH_3; 4-CH_3
85	B10	N	3-CH_3; 4-OCH_3; (A)
86	B10	N	3-CH_3; 4-OCH_3; (B)
87	B2	CH	4-Cl
88	B2	CH	4-F
89	B2	CH	2-OCH_3
90	B2	CH	3-OCH_3
91	B2	CH	3-OCH_3; 4-OCH_3
92	B2	CH	4-$OCH(CH_3)_2$
93	B2	CH	4-$O(CH_2)_2CH_3$
94	B2	CH	4-CH_3
95	B2	CH	4-OC_2H_5
96	B2	CH	4-$O(CH_2)_3CH_3$
97	B3	CH	3-OCH_3; 4-OH; oxalic acid (1:1)
98	B2	CH	2-OCH_3; 5-OCH_3
99	B3	CH	4-$N(CH_3)_2$
100	B2	CH	3-CH_3
116	B2	CH	3-Cl; 4-OCH_3
117	B3	CH	3-Cl; 4-OH
118	B2	CH	3-Cl; 4-OC_2H_5
119	B2	CH	3-OCH_3; 5-OCH_3
120	B2	CH	2-$OCH_2C_6H_5$; 5-OCH_3
121	B3	CH	4-(2-pyridinylmethoxy)
122	B2	CH	2-OCH_3; 5-CH_3
123	B2	CH	3-CH_3; 4-OCH_3
124	B3	CH	2-OH; 5-CH_3
125	B2	CH	3-CH_3; 4-OC_2H_5
126	B3	CH	2-OCH_3; 4-OCH_3
127	B3	CH	4-(4-pyridinylmethoxy)
128	B3	CH	3-OC_2H_5; 4-$OCH_2C_6H_5$
129	B3	CH	2-CH_3; 4-OH
130	B3	CH	4-(3-pyridinylmethoxy)
779	B3	CH	3-OH
780	B34	CH	3-OH; (A); oxalic acid (1:1)
781	B34	CH	3-OH; (B); oxalic acid (1:1)
782	B34	N	3-OCH_3; 4-CH_3; (A)
783	B34	N	3-OCH_3; 4-CH_3; (B)

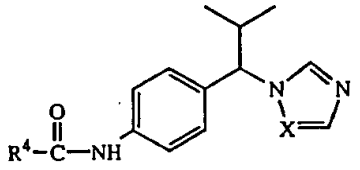
Table 3



Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
131	B2	N	4-Cl
132	B2	N	4-F
133	B2	N	4-CH_3
134	B3	N	4-OH
142	B3	CH	3-OCH_3; 4-OH
143	B3	CH	3-Cl; 4-Cl
144	B2	CH	4-NO_2; (A)
145	B7	CH	4-NH_2; (A)

Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt	Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
135	B2	N	4-OC_2H_5	146	B2	CH	4-NO_2; (B)
136	B2	N	3-OCH_3; 4-OCH_3; hydrate (1:1)	147	B7	CH	4-NH_2; (B)
137	B3	N	3-OH	148	B3	CH	3-I; 4-NH_2
138	B3	N	3-OCH_3; 4-OH	149	B3	CH	3-I; 4-NH_2; (B)
139	B2	CH	3-OCH_3; 4-OCH_3; 5-OCH_3	150	B3	CH	3-I; 4-NH_2; (A)
140	B2	CH	3-OCH_3; 4-OCH_3	151	B2	CH	4-NO_2
141	B3	CH	2-Cl; 4-Cl	152	B7	CH	4-NH_2

Table 4



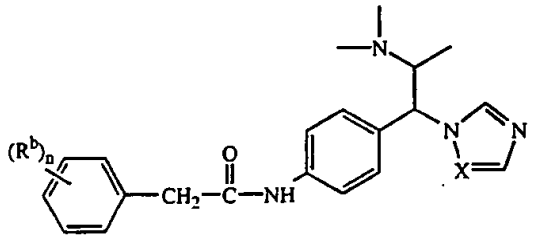
Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
153 (B1)	N; CH_3	216 (B3)	CH; 2-quinoxalinyl
154 (B2)	N; $C(CH_3)=CHC_6H_5$; (E)	217 (B2)	CH; 3,4-dihydro-2*H*-1-benzopyran-2-yl
155 (B2)	N; $CH=CHC_6H_5$; (E)	218(B6a)	CH; $(CH_2)_3C(=O)OH$
156 (B2)	N; $C(CH_3)=CH(3\text{-}Cl\text{-}C_6H_4)$; (E)	219(B6b)	CH; $(CH_2)_3C(=O)OC_2H_5$
157 (B2)	N; $C(CH_3)=CH(4\text{-}F\text{-}C_6H_4)$; (E)	220 (B2)	CH; 5-bromo-2-furanyl
158 (B2)	N; $C(CH_3)=CH$(4-pyridinyl); (E)	221 (B2)	CH; 3-F-C_6H_4
159 (B2)	N; $C(CH_3)=CH(4\text{-}CF_3\text{-}C_6H_4)$; (E)	222 (B3)	CH; $C(CH_3)_2[O(4\text{-}Cl\text{-}C_6H_4)]$
160 (B2)	N; $CF=CHC_6H_5$; (Z)	223 (B3)	CH; $CH_2\text{-}S\text{-}C_6H_5$
161 (B2)	N; 1,3-benzodioxolan-2-yl	224 (B3)	CH; (2-pyrimidinylthio)methyl
162 (B2)	N; (2,3-dihydro-1,4-benzodioxin-2-yl)methyl	225 (B3)	CH; 5-methyl-2-pyrazinyl
163 (B2)	CH; C_2H_5	226 (B2)	CH; 3-methyl-2-furanyl
164 (B4)	CH; $CH(CH_3)\text{-}CH_2(C_6H_5)$	227 (B3)	CH; 4-quinolinyl
165 (B2)	CH; $CH(CH_3)\text{-}CH=CHC_6H_5$; (E)	228 (B3)	CH; 1,2-dihydro-2(1*H*)-pyridinone-3-yl
166 (B2)	CH; C_6H_5	229 (B3)	CH; 1-isoquinolinyl
167 (B2)	CH; 2-benzofuranyl	230 (B2)	CH; 2,3-dihydro-1,4-benzodioxin-5-yl

Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
168 (B2)	CH; 2-benzothienyl	231 (B2)	CH; 3,4-$(OCH_3)_2$-C_6H_3
169 (B2)	CH; 2-furanyl	232 (B2)	CH; 1,3-benzodioxolan-5-yl
170 (B2)	CH; 2-pyrazinyl	233 (B3)	CH; 5-quinoxalinyl
171 (B2)	CH; $C(CH_3)=C(C_6H_5)$ (3-pyridinyl); (E+Z)	234 (B2)	CH; 1,4-benzodioxin-2-yl
172 (B2)	CH; 3-furanyl	235 (B2)	CH; 2-furanylmethyl
173 (B2)	CH; 3-thienyl	236 (B3)	CH; $C(OH)(CH_3)_2$
174 (B2)	CH; 1-cyclohexenyl	237 (B2)	CH; (2,3-dihydro-1,4-benzodioxin-2-yl)methyl
175 (B2)	CH; 2,3-dihydro-1,4-benzo-dioxin-2-yl	238 (B2)	CH; 4-(C_6H_5)-C_6H_4
176 (B2)	CH; $C(CH_3)=C(C_6H_5)(CH_3)$; (E)	239 (B3)	CH; (4-pyridinylthio)methyl
177 (B5)	CH; H	240 (B3)	CH; (2-naphtalenyl)methyl
178 (B2)	CH; 2-indolyl	241 (B3)	CH; 3-quinolinyl
179 (B2)	CH; 2-naphtalenyl	242 (B3)	CH; 3,5-dimethyl-4-isoxazolyl
180 (B2)	CH; 1-methyl-2-indenyl	243 (B2)	CH; 2,3-dihydro-1,4-benzoxathiin-2-yl
181 (B2)	CH; 2-oxolanyl	244 (B3)	CH; 2-thienylmethyl
182 (B2)	CH; 1-naphtalenyl	245 (B3)	CH; 3-thienylmethyl
183 (B2)	CH; OC_2H_5	246 (B3)	CH; 1-naphtalenylmethyl
184 (B2)	CH; 1-methylbenzotriazol-6-yl	247 (B3)	CH; 2-pyridinylmethyl
185 (B2)	CH; 3-oxolanyl	248 (B2)	CH; 1,3-benzodioxolan-2-yl
186 (B2)	CH; 2-phenyl-4-thiazolyl	249 (B3)	CH; $CH(OH)-CH_3$
187 (B2)	CH; 2-thienyl	250 (B3)	CH; 5-methyl-3-phenyl-4-isoxazolyl
188 (B2)	CH; $(CH_2)_2CH_2Cl$	251 (B3)	CH; 3-pyridinylmethyl
189 (B2)	CH; $C(CH_3)(C_6H_5)_2$	252 (B2)	CH; 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl
190 (B2)	CH; 1-C_6H_5-cyclopropyl	253 (B2)	CH; 3,4-dihydro-2*H*-1-benzopyran-3-yl
191 (B2)	CH; 1-C_6H_5-cyclopentyl	254 (B2)	CH; 2*H*-1-benzopyran-3-yl
192 (B2)	CH; cyclopentyl	255 (B2)	CH;(2,3-dihydro-1,4-benzodioxin-6-yl)methyl
193 (B2)	CH; cyclohexyl	256 (B2)	CH;(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)methyl
194 (B3)	CH; 4-pyridinyl	257 (B1)	CH; CH_3; (A)

Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
195 (B3)	CH; 1-methyl-2-pyrrolyl
196 (B3)	CH; 3-pyridinyl
197 (B2)	CH; 2-methylcyclopropyl
198 (B3)	CH; C≡C(C_6H_5)
199 (B3)	CH; cyclopropyl
200 (B2)	CH; 1-C_6H_5-cyclohexyl
201 (B2)	CH; 1-methylcyclohexyl
202 (B2)	CH; 2-methylcyclohexyl
203 (B3)	CH; C(CH_3)=C(C_6H_5)-C_2H_5; (Z)
204 (B2)	CH; 2-phenylcyclopropyl; oxalic acid (1:1)
205 (B2)	CH; 3.4-dihydro-2(1*H*)-quinolinone-6-yl
206 (B2)	CH; OC_6H_5
207 (B3)	CH; C(CH_3)=C(C_6H_5)(2-furanyl);(E)
208 (B3)	CH; 2-pyridinyl
209 (B2)	CH; CH(CH_3)CH_3
210 (B3)	CH; CH_2-S-$CH_2C_6H_5$
211 (B3)	CH; CH_2-OC_6H_5
212 (B3)	CH; CH_2-OCH_3
213 (B3)	CH; CH_2-NH-C_6H_5
214 (B3)	CH; 6-quinoxalinyl
215 (B3)	CH; 2-quinolinyl

Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
258 (B1)	CH; CH_3; (B)
259 (B8)	CH; CH_2(3-iodo-4-azido-C_6H_3); (B)
260 (B8)	CH; CH_2(3-iodo-4-azido-C_6H_3); (A)
261 (B3)	CH; CH_2-NH-C(=O)-C_6H_5
262 (B3)	CH; CH_2-NH-C(=O)-O-CH_2-C_6H_5
263(B23)	CH; N(CH_3)-CH_2-C_6H_5
264(B6a)	CH; CH_2-[1-(CH_2COOH)cyclopentyl]
265(B6a)	CH; $(CH_2)_2$-C(=O)-OH
266(B30)	CH; NH_2
267(B23)	CH; NH-CH_3
268(B23)	CH; NH-C(CH_3)$_2$
269(B23)	CH; NH-CH_2-C_6H_5
270(B23)	CH; NH-(3-pyridinyl)
271(B23)	CH; NH-(2-pyrazinyl)
272(B31)	CH; NH-(1-naphtalenyl)
273(B23)	CH; NH-CH_2-(4-Cl-C_6H_4)
274(B23)	CH; NH-(2-pyridinyl)
275(B23)	CH; NH-(4-pyridinyl)
276(B23)	CH; NH-(6-benzodioxanyl)
277(B23)	CH; NH-(1-CH_3-2-benzimidazolyl)

Table 5

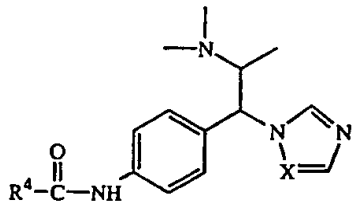


Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
278	B2	N	3-OCH_3;4-OCH_3; (A)

Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
301	B3	CH	3-OC_2H_5; 4-OC_2H_5; (B)

Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt	Co. No.	Ex. No.	X	$(R^b)_n$; stereochemical descriptor if not racemic and/or addition salt
279	B3	N	3-Cl; 4-OCH_3; (A)	302	B3	CH	3,4,5-$(OCH_3)_3$; (A)
280	B3	N	3-CH_3; 4-CH_3; (B)	303	B3	CH	3-Cl; 4-OH; (A)
281	B3	N	4- OCH_3; 3-CH_3; (B)	304	B2	CH	3-Cl; 4-OCH_3; (A)
282	B3	N	3-CH_3; 4-CH_3; (A)	305	B3	CH	3-Cl; 4-OCH_3; (B)
283	B3	N	4-Cl; (B)	306	B3	CH	3-CH_3; 4-CH_3; (B)
284	B3	N	3-Cl; 4-OH; (A)	307	B3	CH	3-Cl; 4-OH; (B)
285	B3	N	3-OC_2H_5; 4-OC_2H_5; (A)	308	B3	CH	3-CH_3; 4-CH_3; 5-CH_3; (A)
286	B3	N	3-CH_3; 4-OCH_3; (A)	309	B3	CH	3-CH_3; 4-CH_3; 5-CH_3; (B)
287	B3	N	3-OCH_3; 4-OCH_3; (B)	310	B3	CH	3-OCH_3; 4-Cl; (A)
288	B3	N	3-Cl; 4- OCH_3; (B)	311	B3	CH	3-OCH_3; 4-Cl; (B)
289	B3	N	3-Cl; 4-OH; (B)	312	B3	CH	3-CH_3; 4-OCH_3; (A)
290	B3	N	3-CH_3; 4-CH_3; 5-CH_3; (A)	313	B3	CH	3-CH_3; 4-OCH_3; (B)
291	B3	N	3-CH_3; 4-CH_3; 5-CH_3; (B)	314	B3	CH	3-OCH_3;4-CH_3; (A)
292	B3	N	3,4,5-$(OCH_3)_3$; (B)	315	B3	CH	3-OCH_3;4-CH_3; (B)
293	B3	N	3-OC_2H_5; 4-OC_2H_5; (B)	316	B3	CH	4-$OCH(CH_3)_2$; (B)
294	B3	N	3-OCH_3; 4-CH_3; (A)	317	B3	CH	4-$N(CH_3)_2$; (A)
295	B3	N	3-OCH_3; 4-CH_3; (B)	318	B3	CH	3-OCH_3;4-OCH_3; (A)
296	B3	N	3-OCH_3; 4-Cl; (A)	319	B3	CH	4-$O(CH_2)_3CH_3$; (A)
297	B3	N	3-OCH_3;4-Cl; (B)	320	B3	CH	4-$O(CH_2)_3CH_3$; (B)
298	B10	N	3-Cl; 4-OH; (A,A)	321	B3	CH	4- $OCH(CH_3)_2$; (A)
299	B10	N	3-Cl; 4-OH; (A,B)	784	B34	N	4-Cl; (B,A)
300	B3	CH	3-OC_2H_5; 4-OC_2H_5; (A)	785	B34	N	4-Cl; (B,B)

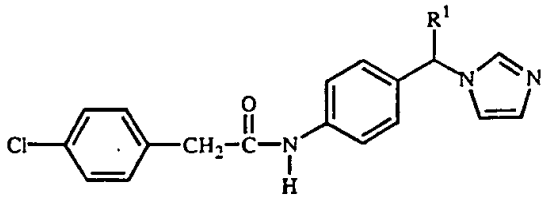
Table 6



Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
322 (B3)	N; (2,3-dihydro-1,4-benzodioxin-6-yl)methyl; (A)	339 (B3)	CH; (2,3-dihydro-1,4-benzodioxin-6-yl)methyl; (B)
323 (B2)	N; OC_6H_5; (A)	340 (B2)	CH; (1,3-benzodioxolan-5-yl) methyl; (A)
324 (B2)	N; 3,4-diOCH_3-C_6H_3; (A)	341 (B3)	CH; 3,4-diOCH_3-C_6H_3; (A)

Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	X; R^4; stereochemical descriptor if not racemic and/or addition salt
325 (B2)	N; (1,3-benzodioxolan-5-yl)-methyl;(A)	342 (B3)	CH; 3,4-diOCH_3-C_6H_3; (B)
326 (B3)	N; $(CH_2)_3$(3,4-diOCH_3-C_6H_3); (A)	343 (B2)	CH; OC_6H_5; (A)
327 (B3)	N; 3,4-diOCH_3-C_6H_3; (B)	344 (B2)	CH; OC_6H_5
328 (B3)	N; $(CH_2)_2$(3,4-diOCH_3-C_6H_3); (B)	345 (B5)	CH; H; (A)
329 (B3)	N; $(CH_2)_3$(3,4-diOCH_3-C_6H_3); (B)	346 (B3)	CH; $(CH_2)_2$(4-OC_2H_5-C_6H_4); (A)
330 (B3)	N; (1,3-benzodioxolan-5-yl)methyl;(B)	347 (B9)	CH; 4-methylpiperazinyl; (A)
331 (B5)	N; H; (B)	348 (B3)	CH; $(CH_2)_2$(4-OC_2H_5-C_6H_4)
332 (B3)	N; $C(CH_3)$=$CH(C_6H_5)$; [B-(E)]	349 (B9)	CH; 4-methylpiperazinyl; (B)
333 (B3)	N; (2,3-dihydro-1,4-benzodioxin-6-yl)methyl; (B)	350 (B3)	CH; CH[O(2-OCH_3-C_6H_4)]; (A)
334 (B2)	N; OC_6H_5; (B)	351 (B3)	CH; CH[O(2-OCH_3-C_6H_4)]; (B)
335 (B5)	N, H; (A)	352 (B3)	CH; (4-CH_3-piperazinyl)methyl; (A)
336 (B3)	CH; $(CH_2)_3$(3,4-diOCH_3-C_6H_3); (B)	353 (B3)	CH; (4-CH_3-piperazinyl)methyl; (B)
337 (B3)	CH; (1,3-benzodioxolan-5-yl)-methyl; (B)	354 (B3)	CH; (4-CH_3-piperazinyl)ethyl
338 (B3)	CH; (2,3-dihydro-1,4-benzodioxin-6-yl)methyl; (A)		

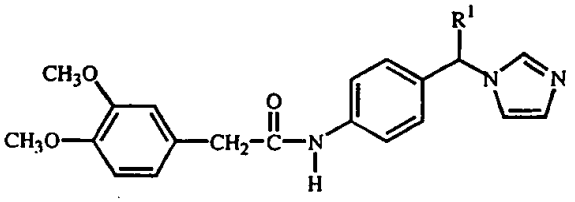
Table 7



Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt
355 (B2)	$(CH_2)_2CH(CH_3)_2$	367 (B2)	$CH[N(CH_3)_2]CH_3$; (A)
356 (B3)	4-Cl-C_6H_4	368 (B2)	$CH[N(CH_3)_2]CH_3$; (B)
357 (B2)	C_6H_5	369 (B2)	$CH(S\text{-}C_6H_5)CH_3$; (B)
358 (B2)	CH_3	370 (B2)	$CH(O\text{-}C_6H_5)CH_3$; (A)
359 (B2)	$CH_2CH(CH_3)_2$	371 (B2)	$CH(CH_3)CH_2CN$; (A+B)
360 (B2)	CH_2-$C(CH_3)_3$	372 (B2)	C_2H_5
361 (B2)	3-CF_3-C_6H_4	373 (B2)	5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl

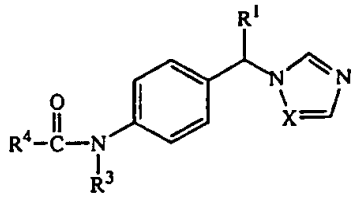
Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt
362 (B2)	cyclohexyl	374 (B2)	$CH(CH_3)C_3H_7$; (B)
363 (B2)	$(CH_2)_2CH_3$	375 (B2)	$CH_2[N(CH_3)_2]$
364 (B2)	$CH(CH_3)CH_2CH_3$	376 (B2)	$CH(S\text{-}C_6H_5)CH_3$; (A)
365 (B2)	$C(CH_3)_3$	377 (B2)	$CH(CH_3)CH_2C_6H_5$
366 (B3)	1-(1-piperidinyl)ethyl; (A)		

Table 8



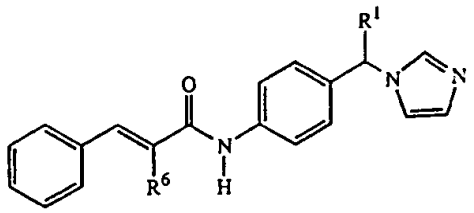
Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt
378 (B2)	$CH(C_3H_7)_2$	399 (B3)	$CH[N(CH_3)(CH_2C_6H_5)]CH_3$
379 (B3)	$CH(CH_3)[N(CH_3)_2]$; (B)	400(B19)	$CH[NH(CH_3)]CH_3$; (A)
380 (B3)	$CH_2[N(CH_3)_2]$	401(B19)	$CH[NH(CH_3)]CH_3$; (B); hydrate (1:1)
381 (B3)	$CH[C(=O)OC_2H_5]CH_3$; (A)	402(B20)	$CH(OH)CH_3$; (B) ; hydrate (1:1)
382 (B3)	$CH[C(=O)OC_2H_5]CH_3$; (B)	403(B18)	$(CH_2)_2(OH)$
383 (B3)	$CH[N(C_2H_5)_2]CH_3$; (B)	404(B21)	$CH(CH_3)CH_2OCH_3$; (A)
384 (B3)	$CH(CH_3)C_5H_{11}$; (A)	405(B21)	$CH(CH_3)CH_2OCH_3$; (B)
385 (B3)	$CH(CH_3)C_5H_{11}$; (B)	406 (B3)	$CH[N(CH_3)(C_4H_9)]CH_3$; (A)
386(B18)	$CH(CH_3)CH_2OH$; (A)	407 (B3)	$CH[N(CH_3)[(CH_2)_2N(CH_3)_2]]CH_3$; (A)
387 (B3)	$CH[N(C_2H_5)_2]CH_3$; (A)	408 (B3)	1-(4-morpholinyl)ethyl; (A)
388 (B3)	$CH[N(CH_3)_2]C_2H_5$; (B)	409 (B3)	1-(4-morpholinyl)ethyl; (B)
389 (B3)	$[1\text{-}CH_3\text{-}2\text{-}(1\text{-piperidinyl})]C_2H_5$; (B)	410 (B3)	1-methyl-3-piperidinyl; (A)
390 (B3)	$[1\text{-}CH_3\text{-}2\text{-}(1\text{-piperidinyl})]C_2H_5$; (A)	411 (B3)	1-methyl-2-piperidinyl; (A)
391 (B3)	$CH(CH_3)[CH_2[N(CH_3)_2]]$; (B)	412 (B3)	1-(4-methyl-1-piperazinyl)ethyl; (A); hydrate (1:1)
392 (B3)	$CH(CH_3)[CH_2[N(CH_3)_2]]$; (A)	413 (B3)	$CH[N(CH_3)(C_3H_7)]CH_3$; (A)
393 (B3)	$[1\text{-}N(CH_3)_2]C_3H_7$; (A)	414 (B3)	$CH[N(CH_3)(C_3H_7)]CH_3$; (B)
394(B18)	$(1\text{-}CH_3)C_2H_5OH$; (B)	415 (B3)	$CH[N(CH_3)[(CH_2)_2C_6H_5]]CH_3$
395 (B3)	$CH_2C(=O)OC_2H_5$	416 (B3)	$CH[N(CH_3)(C_2H_5)]CH_3$; (A)
396 (B3)	$CH[N(CH_3)(CH_2C_6H_5)]CH_3$; (B)	417 (B3)	$CH[OC(=O)N(CH_2C_6H_5)_2]CH_3$; (A)
397(B17)	CH_2OCH_3	418 (B3)	$CH[N(CH_2C_6H_5)_2]CH_3$; (B)
398 (B3)	$CH[N(CH_3)(CH_2C_6H_5)]CH_3$; (A)	419 (B3)	$CH[N(CH_2C_6H_5)_2]CH_3$; (A)

Table 9



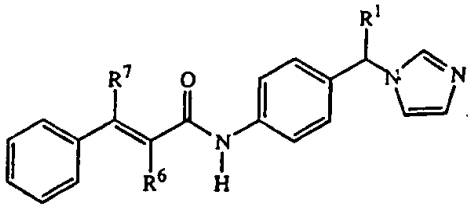
Co. No.	Ex. No.	X	R^1	R^3	R^4; stereochemical descriptor if not racemic and/or addition salt
420	B3	CH	C_6H_5	H	$CH(OH)C_6H_5$
421	B2	CH	$CH(CH_3)_2$	CH_3	$C(CH_3)=CHC_6H_5$; (E)
422	B2	CH	$CH(CH_3)_2$	C_2H_5	$C(CH_3)=CHC_6H_5$; (E)
423	B3	CH	4-Cl-C_6H_4	H	$CH(OH)C_6H_5$
424	B2	CH	C_6H_5	H	2-pyrazinyl
425	B2	CH	C_6H_5	H	2,3-dihydro-1,4-benzodioxin-2-yl
426	B2	CH	C_6H_5	H	(2,3-dihydro-1,4-benzodioxin-2-yl)-methyl
427	B2	CH	$CH(C_2H_5)_2$	CH_3	CH_2(3,4-diOCH_3-C_6H_3)
428	B3	CH	$CH[N(CH_3)_2]CH_3$	H	CH_2(3,4,5-triOCH_3-C_6H_2); (B)
429	B3	CH	$CH[N(CH_3)_2]CH_3$	H	$(CH_2)_2$(3,4-diOCH_3-C_6H_3); (B)
430	B3	CH	$CH[N(CH_3)_2]CH_3$	H	$(CH_2)_2$(3,4-diOCH_3-C_6H_3); (A)
431	B3	CH	$CH[N(CH_3)_2]CH_3$	H	$(CH_2)_3$(3,4-diOCH_3-C_6H_3); (A); oxalic acid (1:1)
432	B3	CH	2-butyl	H	CH_2(3-OCH_3-4-OH-C_6H_3)
433	B3	CH	$CH_2[N(CH_3)_2]$	H	CH_2(3,4-diCH_3-C_6H_3)
434	B3	CH	$CH_2[N(CH_3)_2]$	H	3,4-diOCH_3-C_6H_3
435	B2	CH	$CH_2[N(CH_3)_2]$	H	OC_6H_5
436	B9	CH	$CH_2[N(CH_3)_2]$	H	4-methyl-1-piperazinyl
437	B2	N	$CH(CH_3)[N(CH_3)_2]$	CH_3	CH_2(3,4-diOCH_3-C_6H_3); (B)
438	B2	N	$CH(CH_3)[N(CH_3)_2]$	CH_3	CH_2(3,4-diOCH_3-C_6H_3); (A)
439	B2	CH	$CH(CH_3)[N(CH_3)_2]$	CH_3	CH_2(3,4-diOCH_3-C_6H_3); (A)

Table 10



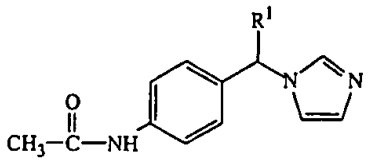
Co No (Ex No)	R^1; R^6; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; R^6; stereochemical descriptor if not racemic and/or addition salt
440 (B2)	4-Cl-C_6H_4; H	472 (B3)	$CH(CH_3)_2$; cyclopentyl; (E)
441 (B2)	3-Cl-C_6H_4; H	473 (B3)	$CH(CH_3)_2$; cyclohexyl; (E)
442 (B2)	3-F-C_6H_4; H	474 (B2)	$CH_2CH(CH_3)_2$; CH_3; (E)
443 (B2)	4-F-C_6H_4; H	475 (B2)	$(CH_2)_2CH(CH_3)_2$; CH_3; (E)
444 (B2)	C_6H_5; C_6H_5	476 (B2)	$CH_2C(CH_3)_3$; CH_3; (E); hydrate (2:1)
445 (B2)	C_6H_5; CH_3	477 (B2)	1,3-dioxan-5-yl; CH_3; (E)
446 (B2)	4-F-C_6H_4; CH_3	478 (B2)	$CH(C_2H_5)_2$; CH_3; (E)
447 (B2)	4-Cl-C_6H_4; C_6H_5	479 (B2)	CH=CH-$CH(CH_3)_2$; CH_3; (E,E)
448 (B2)	3-Cl-C_6H_4; CH_3	480 (B2)	$CH(CH_3)C_2H_5$; CH_3; (E)
449 (B2)	3-Cl-C_6H_4; C_6H_5	481 (B2)	$C(CH_3)_3$; CH_3; (E)
450 (B2)	4-F-C_6H_4; C_6H_5	482 (B2)	$CH(CH_3)C_3H_7$; CH_3; [A-(E)]
451 (B2)	4-Cl-C_6H_4; CH_3	483 (B2)	CH(S-C_6H_5)CH_3; CH_3; (A)
452 (B2)	C_6H_5; C_2H_5	484 (B2)	CH(S-C_6H_5)CH_3; CH_3; (B)
453 (B2)	C_6H_5; C_3H_7	485 (B2)	$CH(C_6H_5)_2$; CH_3; (E)
454 (B2)	$CH(CH_3)_2$; C_6H_5	486 (B2)	$CH(C_3H_7)_2$; CH_3; (E)
455 (B2)	$CH(CH_3)_2$; CH_3; (E)	487 (B2)	$CH(CH_3)C_5H_{11}$; CH_3; [A-(E)]
456 (B2)	$CH(CH_3)_2$; 2-CH_3-C_6H_4	488 (B2)	$CH(CH_3)C_5H_{11}$; CH_3; [B-(E)]
457 (B2)	$CH(CH_3)_2$; C_2H_5	489 (B2)	$CH(C_6H_5)CH_3$; CH_3; [A-(E)]
458(B10)	$CH(CH_3)_2$; CH_3; (+)-[A-(E)]	490 (B2)	$CH(C_6H_5)CH_3$; CH_3; [B-(E)]
459(B10)	$CH(CH_3)_2$; CH_3; (-)-[B-(E)]	491 (B2)	5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphtalenyl; CH_3; (E)
460 (B2)	C_2H_5; CH_3; (E)	492 (B2)	$CH(C_2H_5)C_5H_{11}$; CH_3; [A-(E)]
461 (B2)	$CH(CH_3)_2$; F; (E)	493 (B2)	$CH(C_2H_5)C_4H_9$; CH_3; (E)
462 (B2)	C_4H_9; CH_3; (E)	494 (B2)	$CH(C_2H_5)C_5H_{11}$; CH_3; [B-(E)]
463 (B2)	cyclohexyl; CH_3; (E)	495 (B2)	$CH[N(CH_3)_2]CH_3$; CH_3; [A-(E)]
464 (B2)	$CH(CH_3)_2$; C_3H_7; (E)	496 (B3)	$CH[N(CH_3)_2]CH_3$; CH_3; [B-(E)]
465 (B2)	$CH(CH_3)_2$; C_4H_9; (E)	497 (B2)	C_6H_5; H
466 (B2)	CH_3; CH_3; (E)	498 (B2)	H; H
467 (B2)	C_3H_7; CH_3; (E)	499 (B2)	$CH(CH_3)_2$; H
468 (B2)	cyclohexyl; C_6H_5; (E)	500 (B2)	4-Br-C_6H_4; H
469 (B2)	cyclopropyl; CH_3; (E)	501 (B2)	4-CH_3-C_6H_4; H
470 (B2)	cyclopentyl; CH_3; (E)	502 (B2)	$CH(CH_3)_2$; H; (E)
471 (B3)	$CH(CH_3)_2$; $CH(CH_3)_2$; (E)	786 (B3)	2,5-diCl-C_6H_3; CH_3; (E)

Table 11



Co No (Ex No)	R^1; R^6; R^7; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; R^6; R^7; stereochemical descriptor if not racemic and/or addition salt
503 (B2)	C_6H_5; H; C_6H_5	512 (B2)	4-Cl-C_6H_4; H; CH_3
504 (B2)	4-Cl-C_6H_4; H; C_6H_5	513 (B3)	4-Cl-C_6H_4; H; C_4H_9
505 (B2)	3-Cl-C_6H_4; H; C_6H_5	514 (B3)	4-Cl-C_6H_4; H; cyclohexyl; (E+Z)
506 (B2)	4-F-C_6H_4; H; C_6H_5	515 (B3)	4-Cl-C_6H_4; H; $CH(CH_3)_2$; (E+Z)
507 (B2)	4-Cl-C_6H_4; H; C_2H_5	516 (B2)	4-Cl-C_6H_4; H; 3-pyridinyl
508 (B2)	4-F-C_6H_4; H; CH_3	517 (B2)	4-F-C_6H_4; H; 3-pyridinyl
509 (B2)	H; H; C_6H_5	518 (B3)	$CH(CH_3)_2$; CH_3; 3-thienyl; (E+Z)
510 (B2)	CH_3; H; C_6H_5	519 (B3)	$CH(CH_3)_2$; CH_3; C_3H_7; (E+Z)
511 (B2)	$CH(CH_3)_2$; H; C_6H_5	520 (B3)	4-Cl-C_6H_4; H; 3,5-diCl-C_6H_3

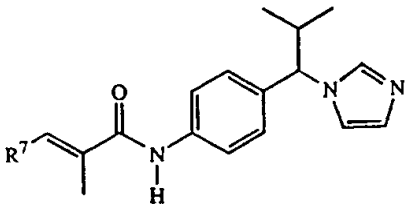
Table 12



Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt
521(B17)	$CH(CH_3)_2$	548 (B1)	$CH_2N(CH_3)_2$
522 (B1)	3-Cl-C_6H_4	549 (B1)	$CH(C_2H_5)(n\text{-}C_4H_9)$
523 (B1)	3-F-C_6H_4	550(B17)	1-(ethoxycarbonyl)ethyl
524 (B1)	3-CF_3-C_6H_4	551 (B1)	$CH[N(CH_3)_2]CH_3$; (A); hydrate (1:1)
525 (B1)	cyclohexyl	552 (B1)	$CH[N(CH_3)_2]CH_3$; (B)
526(B17)	cyclopropyl	553 (B1)	$CH(CH_3)[CH_2(C_6H_5)]$
527(B17)	cyclopentyl	554 (B1)	$CH[N(C_2H_5)_2]CH_3$; (A)
528(B17)	$(CH_2)_2CH(CH_3)_2$	555 (B1)	$CH[N(C_2H_5)_2]CH_3$; (B)
529(B17)	$CH_2C(CH_3)_3$	556 (B1)	$CH[N(C_2H_5)_2]CH_3$
530(B17)	1,3-dioxan-5-yl	557 (B1)	$CH[N(CH_3)_2]C_2H_5$; (A)
531 (B1)	$CH(C_2H_5)_2$	558 (B1)	$CH[N(CH_3)_2]C_2H_5$; (B)

Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1; stereochemical descriptor if not racemic and/or addition salt
532(B17)	$CH{=}CH{-}CH(CH_3)_2$	559 (B1)	$CH[N(CH_3)_2]C_2H_5$
533 (B1)	$CH(CH_3)C_2H_5$	560 (B1)	(ethoxycarbonyl)methyl
534 (B1)	$C(CH_3)_3$	561(B17)	$CH[N(CH_3)(CH_2{-}C_6H_5)]CH_3$
535 (B1)	$CH[N(CH_3)_2]CH_3$; hydrate (1:1)	562 (B1)	$CH[N(CH_3)(n\text{-}C_4H_9)]CH_3$
536 (B1)	$CH(CH_3)(n\text{-}C_3H_7)$	563 (B1)	$CH[N(CH_3)[(CH_2)_2N(CH_3)_2]]CH_3$
537 (B1)	1-(1-piperidinyl)ethyl	564(B17)	1-(4-morpholinyl)ethyl
538 (B1)	$CH(S{-}C_6H_5)CH_3$; (A+B)	565 (B1)	$CH[N(CH_3)_2]C_2H_5$
539 (B1)	$CH(O{-}C_6H_5)CH_3$	566 (B1)	$CH[N(CH_3)(C_2H_5)]CH_3$
540 (B1)	$CH(CH_3)CH_2CN$	567 (B1)	1-methyl-3-piperidinyl
541 (B1)	$CH(C_6H_5)_2$	568 (B1)	1-methyl-2-piperidinyl; (A)
542 (B1)	$CH(C_2H_5)(n\text{-}C_3H_7)$	569 (B1)	1-(4-methyl-1-piperazinyl)ethyl
543 (B1)	$CH(n\text{-}C_3H_7)_2$	570 (B1)	$CH[N(CH_3)(n\text{-}C_3H_7)]CH_3$
544(B17)	$CH(C_6H_5)CH_3$	571 (B1)	$CH[N(CH_3)(C_2H_5{-}C_6H_5)]CH_3$
545(B17)	5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphtalenyl	572 (B1)	$CH[N(CH_2{-}C_6H_5)_2]CH_3$
546(B17)	$CH(CH_3)(n\text{-}C_5H_{11})$	573 (B1)	$CH[OC(=O)N(CH_2{-}C_6H_5)_2]CH_3$
547(B17)	$CH(C_2H_5)(n\text{-}C_5H_{11})$	787(B17)	2,5-diCl-C_6H_3

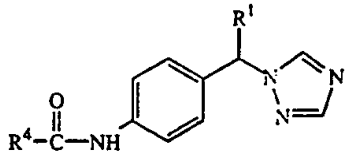
Table 13



Co No (Ex No)	R^7; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^7; stereochemical descriptor if not racemic and/or addition salt
574 (B2)	CH_3; (E)	594 (B2)	2-furanyl; (E)
575 (B3)	3-pyridinyl; (E)	595 (B2)	2-thienyl; (E)
576 (B3)	4-pyridinyl; (E)	596 (B2)	3-thienyl; (E)
577 (B2)	3-Cl-C_6H_4; (E)	597 (B3)	H
578 (B2)	3-CF_3-C_6H_4	598 (B2)	2(1*H*)-quinolinone-6-yl; (E); hydrate (2:1)
579 (B2)	4-Cl-C_6H_4; (E)	599 (B2)	2-methyl-2*H*-benzotriazole-5-yl; (E)
580 (B2)	4-CF_3-C_6H_4; (E)	600 (B2)	2-benzofuranyl; (E)
581 (B2)	cyclohexyl; (E)	601 (B2)	5-methyl-2-furanyl; (E)
582 (B2)	4-OCH_3-C_6H_4; (E)	602 (B2)	1-methyl-1*H*-benzotriazole-6-yl; (E)

Co No (Ex No)	R^7; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^7; stereochemical descriptor if not racemic and/or addition salt
583 (B2)	4-F-C_6H_4; (E)	603 (B2)	2(1*H*)-quinolinone-4-yl; (E)
584 (B2)	3-OCH_3-C_6H_4; (E)	604 (B3)	2-pyridinyl; (E)
585 (B2)	2-F-C_6H_4; (E)	605 (B3)	1-methyl-2-pyrrolyl
586 (B2)	3-F-C_6H_4; (E)	606 (B2)	2,3,5,6-tetra(F)-4-(OC_2H_5)phenyl; (E)
587 (B2)	$(CH_2)_2C_6H_5$; (E)	607 (B2)	2,4-di(F)-C_6H_3; (E)
588 (B2)	$CH(CH_3)_2$; (E)	608 (B2)	3-Br-4-F-C_6H_3; (E)
589 (B2)	$CH_2C_6H_5$; (E)	609 (B2)	2-F-4-CF_3-C_6H_3; (E)
590 (B2)	6-quinolinyl; (E)	610 (B3)	4-NO_2-C_6H_4; (E)
591 (B2)	2-naphtalenyl; (E)	611(B16)	4-NH_2-C_6H_4; (E)
592 (B2)	4-quinolinyl; (E); hydrate (2:1)	612 (B3)	4-(NHC(=O)CH_3)-C_6H_4; (E)
593 (B2)	1-naphtalenyl; (E)		

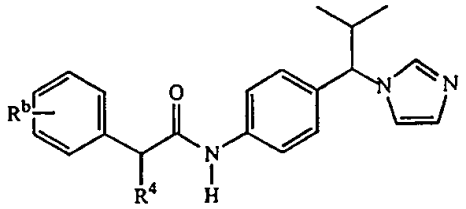
Table 14



Co No (Ex No)	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt
613 (B1)	3-CF_3-C_6H_4; CH_3	632 (B2)	$CH[N(CH_3)_2]CH_3$; $C(CH_3)=CHC_6H_5$; [A-(E)]
614 (B2)	3-CF_3-C_6H_4; $CH_2C_6H_5$	633 (B1)	$CH(CH_3)CH_2C_6H_5$; CH_3
615 (B1)	3-F-C_6H_4; CH_3	634 (B2)	$CH(CH_3)CH_2C_6H_5$; CH_2(4-Cl-C_6H_4)
616 (B1)	3-F-C_6H_4; CH_3	635(B15)	1-(methyl-1-piperidinyl)ethyl; CH_3
617 (B2)	3-CF_3-C_6H_4; $CH=CHC_6H_5$; (E)	636 (B2)	1-(methyl-1-piperidinyl)ethyl; CH_2(4-Cl-C_6H_4)
618 (B2)	3-F-C_6H_4; $CH=CHC_6H_5$; (E)	637 (B1)	$CH(CH_3)$(*n*-C_3H_7); CH_3
619 (B2)	3-F-C_6H_4; $CH_2C_6H_5$	638 (B2)	$CH(CH_3)$(*n*-C_3H_7); CH_2(4-Cl-C_6H_4)
620 (B2)	3-F-C_6H_4; $C(CH_3)=CHC_6H_5$; (E); nitrate (1:1)	639 (B3)	$CH(CH_3)$(*n*-C_3H_7); CH_2(3,4-diOCH_3-C_6H_3)
621 (B2)	$CH(C_2H_5)_2$; 1,3-benzodioxolan-2-yl	640 (B3)	$CH(CH_3)C_2H_5$; CH_2(3,4-diOCH_3-C_6H_3)
622 (B1)	$CH_2C(CH_3)_3$; CH_3	641 (B1)	$C(CH_3)_3$; CH_3
623 (B2)	$CH_2C(CH_3)_3$; CH_2(4-Cl-C_6H_4)	642 (B3)	$C(CH_3)_3$; CH_2(3,4-diOCH_3-C_6H_3); hydrate (1;1)
624 (B2)	$CH[C(=O)OC_2H_5]CH_3$; CH_2(4-Cl-C_6H_4)	643 (B1)	CH(*n*-C_3H_7)$_2$; CH_3

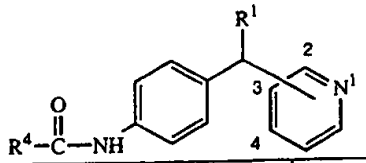
Co No (Ex No)	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt
625 (B1)	$CH(CH_3)C_2H_5$; CH_3
626 (B2)	$CH(CH_3)C_2H_5$; $CH_2(4\text{-}Cl\text{-}C_6H_4)$
627 (B1)	$CH[N(CH_3)_2]CH_3$; CH_3; (A)
628 (B2)	$CH[N(CH_3)_2]CH_3$; $CH_2(4\text{-}Cl\text{-}C_6H_4)$; (A)
629 (B3)	$CH[N(CH_3)_2]CH_3$; $(CH_2)_2(3,4\text{-}diOCH_3\text{-}C_6H_3)$; (A)
630 (B3)	$CH[N(CH_3)_2]CH_3$; $CH_2(3,4,5\text{-}triOCH_3\text{-}C_6H_2)$; (A)
631(B15)	$CH[N(CH_3)_2]CH_3$; CH_3; (B)
644 (B2)	$CH(n\text{-}C_3H_7)_2$; $CH_2(3.4\text{-}diOCH_3\text{-}C_6H_3)$
645 (B1)	$CH[N(CH_3)_2]C_2H_5$; CH_3; (A)
646 (B3)	$CH[N(CH_3)_2]C_2H_5$; $CH_2(3,4\text{-}diOCH_3\text{-}C_6H_3)$; (A)
647 (B1)	$CH[N(C_2H_5)_2]CH_3$; CH_3; (A)
648 (B1)	$CH[N(C_2H_5)_2]CH_3$; CH_3; (A+B)
649 (B3)	$CH[N(C_2H_5)_2]CH_3$; $CH_2(3,4\text{-}diOCH_3\text{-}C_6H_3)$; (A)

Table 15



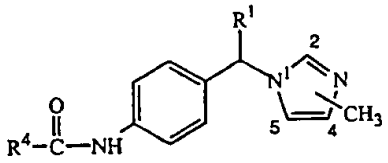
Co No (Ex No)	R^4, R^b; stereochemical descriptor if not racemic and/or addition salt
650 (B2)	H; H
651 (B2)	H; 4-Cl
652 (B2)	H; 3-Cl
653 (B2)	H; 4-F
654 (B2)	H; $3\text{-}CF_3$
655 (B2)	C_6H_5; H
656 (B2)	H; 3-F
657 (B2)	CH_3; H
658 (B2)	$CH(CH_3)_2$; H
659 (B2)	cyclopentyl; H
660 (B2)	C_2H_5; H
661 (B2)	cyclohexyl; H
662 (B2)	H; $4\text{-}OCH_3$
663 (B2)	H; $4\text{-}OC_2H_5$
664 (B2)	H; 2-Cl
665 (B2)	H; $3\text{-}OCH_3$
666 (B3)	H; $4\text{-}CH_3$
667 (B3)	H; 3-OH
668 (B3)	H; 4-OH
669 (B3)	OH; 4-Cl
670 (B3)	OCH_3; H; [R-(R*,R*)]+[R-(R*,S*)]

Table 16



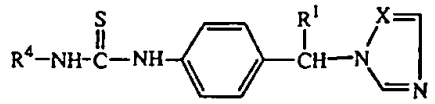
Co No (Ex No)	pyridinyl position	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	pyridinyl position	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt
671(B14)	3	$CH(CH_3)_2$; CH_3	684 (B3)	3	4-Cl-C_6H_4; $CH=C(C_6H_5)(3\text{-Cl-}C_6H_4)$
672 (B2)	3	C_6H_5; $CH=CH\text{-}C_6H_5$	685 (B2)	4	$CH(CH_3)_2$; $CH_2(4\text{-Cl-}C_6H_4)$
673(B12)	3	4-Cl-C_6H_4; CH_3	686 (B3)	3	$CH(CH_3)_2$; $CH_2(4\text{-Cl-}C_6H_4)$
674 (B2)	3	4-Cl-C_6H_4; $CH=CH\text{-}C_6H_5$	687 (B2)	2	$CH(CH_3)_2$; $CH_2(4\text{-Cl-}C_6H_4)$
675 (B2)	3	C_6H_5; $C(CH_3)=CH\text{-}C_6H_5$	688(B13)	2	OH; CH_3
676 (B2)	3	4-Cl-C_6H_4; $CH=C(C_6H_5)_2$	689(B13)	3	OH; CH_3
677 (B3)	4	4-Cl-C_6H_4; $CH=CC_6H_5)_2$	690(B31)	3	$CH(CH_3)_2$; NH(3-F-C_6H_4)
678 (B2)	3	3-F-C_6H_4; $CH=CH\text{-}C_6H_5$	691(B31)	2	$CH(CH_3)_2$; NH(3-F-C_6H_4)
679 (B2)	3	$CH(CH_3)_2$; $C(CH_3)=CH\text{-}C_6H_5$; (E)	692(B31)	4	$CH(CH_3)_2$; NH(3-F-C_6H_4)
680 (B3)	2	4-Cl-C_6H_4; $CH=C(C_6H_5)_2$	788 (B3)	4	H; $CH=C(C_6H_5)(3\text{-Cl-}C_6H_4)$
681 (B2)	4	$CH(CH_3)_2$; $C(CH_3)=CH\text{-}C_6H_5$; (E)	789 (B3)	4	$CH(CH_3)_2$; $CH=C(C_6H_5)(3\text{-Cl-}C_6H_4)$
682 (B2)	2	$CH(CH_3)_2$; $C(CH_3)=CH\text{-}C_6H_5$; (E)	790 (B3)	4	cyclohexyl; $CH=C(C_6H_5)(3\text{-Cl-}C_6H_4)$
683 (B3)	3	4-Cl-C_6H_4; $CH=CH(3\text{-Cl-}C_6H_4)_2$			

Table 17



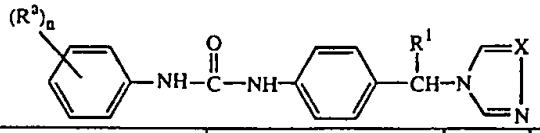
Co No (Ex No)	methyl position	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt	Co No (Ex No)	methyl position	R^1, R^4; stereochemical descriptor if not racemic and/or addition salt
693 (B2)	5	4-Cl-C_6H_4; $CH=C(C_6H_5)(3\text{-Cl-}C_6H_4)$; (E+Z)	695 (B2)	2	$CH(CH_3)_2$; $CH_2(4\text{-Cl-}C_6H_4)$
694 (B1)	2	$CH(CH_3)_2$; CH_3			

Table 18



Co. No.	Ex. No.	R^1	R^4	X	Stereochemical descriptor if not racemic and/or addition salt
696	B31	$CH(CH_3)_2$	CH_3	CH	
697	B31	$CH(CH_3)_2$	C_6H_5	CH	
698	B25	$CH(CH_3)_2$	$C_6H_5.C(=O)$-	CH	
699	B22a B22b	$CH(CH_3)_2$	H	CH	
700	B31	$CH(CH_3)_2$	2F-C_6H_4	CH	
701	B31	$CH(CH_3)_2$	3F-C_6H_4	CH	
702	B25	$CH(C_2H_5)_2$	C_6H_5-C(=O)-	CH	
703	B22a	$CH(C_2H_5)_2$	H	CH	
704	B27	$CH(CH_3)[N(CH_3)_2]$	2-benzothiazolyl	CH	(A)
705	B27	$CH(C_2H_5)_2$	2-benzothiazolyl	CH	
706	B27	$CH(C_2H_5)_2$	2-benzothiazolyl	N	
791	B25	2,5-diCl-C_6H_3	C_6H_5-C(=O)-	CH	
792	B22a	2,5-diCl-C_6H_3	H	H	

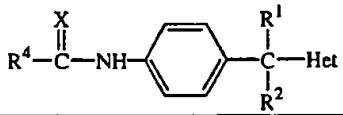
Table 19



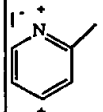
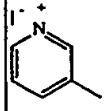
Co. No.	Ex. No.	$(R^a)_n$	R^1	X	Stereochemical descriptor if not racemic
707	B31	4-(O-C_2H_5)	$CH(CH_3)_2$	CH	
708	B23	3,4-di(OCH_3)	$CH(CH_3)_2$	CH	
709	B31	2,5-di(F)	3-(CF_3)-C_6H_4	CH	
710	B31	2,5-di(F)	$CH(C_2H_5)_2$	CH	
711	B31	3-F	3-(CF_3)-C_6H_4	N	
712	B31	2,5-di(F)	$CH(C_2H_5)_2$	N	
713	B31	2-F	$CH(C_2H_5)_2$	CH	
714	B31	2-F	3-(CF_3)-C_6H_4	CH	
715	B31	2-F	$CH(C_2H_5)_2$	N	
716	B31	4-OCH_3	3-(CF_3)-C_6H_4	CH	

Co. No.	Ex. No.	$(R^a)_n$	R^1	X	Stereochemical descriptor if not racemic
717	B23	3,4-di(OCH_3)	$CH(CH_3)[N(CH_3)_2]$	N	(A)
718	B23	3,4-di(OCH_3)	$CH(C_2H_5)_2$	N	
719	B23	3,4-di(OCH_3)	$CH(CH_3)[N(CH_3)_2]$	CH	(A)
720	B23	3,4-di(OCH_3)	$CH(CH_3)[N(CH_3)_2]$	N	(B)
721	B23	3,4-di(OCH_3)	CH_2- $N(CH_3)_2$	CH	
722	B31	4-OCH_3	$CH(CH_3)_2$	CH	
723	B31	3-F	$CH(C_2H_5)_2$	N	
724	B31	3-F	$CH(C_2H_5)_2$	CH	
725	B31	3-F	$CH(CH_3)_2$	N	
726	B31	2-F	$CH(CH_3)_2$	CH	
727	B7	3-NH_2	$CH(CH_3)_2$	CH	
728	B31	2,5-di(F)	$CH(CH_3)_2$	CH	
729	B31	3-F	3-(CF_3)-C_6H_4	CH	
730	B31	3-CF_3	$CH(CH_3)_2$	CH	
731	B31	3-F	4-Cl-C_6H_4	CH	
732	B31	3,4-di(Cl)	$CH(CH_3)_2$	CH	
733	B31	3-OCH_3	$CH(CH_3)_2$	CH	
734	B31	2,4-di(F)	$CH(CH_3)_2$	CH	
735	B31	3-F	C_6H_5	CH	
736	B31	3-CH_3	$CH(CH_3)_2$	CH	
737	B31	3-NO_2	$CH(CH_3)_2$	CH	
738	B31	3-Cl	$CH(CH_3)_2$	CH	
739	B31	4-Cl	$CH(CH_3)_2$	CH	
740	B31	4-F	$CH(CH_3)_2$	CH	
741	B31	3-F	$CH(CH_3)_2$	CH	
742	B31	H	$CH(CH_3)_2$	CH	

Table 20

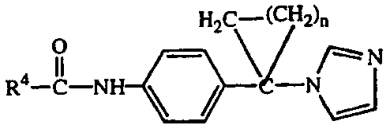


Co.No. (Ex.No.)	R^1	R^2	R^4	X	Het	Stereochemical descriptor if not racemic
743(B29)	$CH(CH_3)_2$	H	NH_2	N-C_6H_5	1*H*-1-imidazolyl	
744(B29)	$CH(CH_3)_2$	H	NH_2	N-(3F-	1*H*-1-imidazolyl	

Co.No. (Ex.No.)	R^1	R^2	R^4	X	Het	Stereochemical descriptor if not racemic
				C_6H_4)		
745 (B2)	$CH(CH_3)_2$	$CH(CH_3)_2$	$-CH_2-(4-Cl-C_6H_4)$	O	1,2,4-triazol-1-yl	
746(B31)	$CH(CH_3)_2$	$CH(CH_3)_2$	$-NH-(3-F-C_6H_4)$	O	1*H*-1-imidazolyl	
747 (B1)	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_3	O	1,2,4-triazol-1-yl	
748 (B1)	$CH(CH_3)_2$	H	CH_3	O	1,2,4-triazol-4-yl	
749 (B2)	$CH(CH_3)_2$	H	$-C(CH_3)=CH-C_6H_5$	O	1,2,4-triazol-4-yl	
750 (B1)	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_3	O	1*H*-1-imidazolyl	
751 (B2)	$CH(CH_3)_2$	$CH(CH_3)_2$	$-C(CH_3)=CH-C_6H_5$	O	1*H*-1-imidazolyl	(E)
752(B17)	CH_3	CH_3	CH_3	O	1*H*-1-imidazolyl	
753 (B2)	CH_3	CH_3	$-C(CH_3)=CH-C_6H_5$	O	1*H*-1-imidazolyl	
754 (B1)	$CH(CH_3)_2$	C_2H_5	CH_3	O	1*H*-1-imidazolyl	
755 (B2)	$CH(CH_3)_2$	C_2H_5	$(4-Cl-C_6H_4)-CH_2-$	O	1*H*-1-imidazolyl	
756 (B1)	C_2H_5	C_2H_5	CH_3	O	1*H*-1-imidazolyl	
757 (B1)	$CH(C_2H_5)_2$	$CH(CH_3)_2$	CH_3	O	1*H*-1-imidazolyl	
758 (B2)	$CH(CH_3)_2$	C_2H_5	$-C(CH_3)=CH-C_6H_5$	O	1*H*-1-imidazolyl	(E)
759 (B1)	$CH(CH_3)_2$	CH_3	CH_3	O	1*H*-1-imidazolyl	
760 (B1)	$CH(CH_3)_2$	n-C_4H_9	CH_3	O	1*H*-1-imidazolyl	
761 (B2)	$CH(CH_3)_2$	n-C_4H_9	$-C(CH_3)=CH-C_6H_5$	O	1*H*-1-imidazolyl	(E)
762 (B2)	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_2-[3,4-di-(OCH_3)-C_6H_3]	O	1*H*-1-imidazolyl	
763 (B2)	$CH(CH_3)_2$	$CH(CH_3)_2$	$-CH_2-(4-Cl-C_6H_4)$	O	1*H*-1-imidazolyl	
764(B28)	$CH(CH_3)_2$	H	$-CH_2-(4-Cl-C_6H_4)$	S	1*H*-1-imidazolyl	
765 (B9)	$CH(C_2H_5)_2$	n-C_3H_7	CH_3	O	1*H*-1-imidazolyl	
766 (B2)	$CH(C_2H_5)_2$	n-C_3H_7	$-CH_2-(4-Cl-C_6H_4)$	O	1*H*-1-imidazolyl	
767 (B1)	$CH(C_2H_5)_2$	C_2H_5	CH_3	O	1*H*-1-imidazolyl	
768 (B2)	$CH(C_2H_5)_2$	C_2H_5	$-CH_2-(4-Cl-C_6H_4)$	O	1*H*-1-imidazolyl	
769(B25)	OH	H	CH_3	O		
770(B25)	OH	H	CH_3	O		
771(B24)	OH	$CH(CH_3)$-$N(CH_3)_2$	CH_3	O	1-methyl-5-imidazolyl	
772(B24)	OH	$CH(C_2H_5)_2$	CH_3	O	1-methyl-5-imidazolyl	

Co.No. (Ex.No.)	R^1	R^2	R^4	X	Het	Stereochemical descriptor if not racemic
773(B31)	$CH(CH_3)_2$	H	-NH-(3-F-C_6H_4)	O	2-methyl-1-imidazolyl	
793(B33)	4-Cl-C_6H_4	H	H	O	1-methyl-5-imidazolyl	
794(B3)	4-Cl-C_6H_4	OH	CH(OH)(3-Cl-C_6H_4)	O	1-methyl-5-imidazolyl	
795(B3)	4-Cl-C_6H_4	H	CH(OH)(3-Cl-C_6H_4)	O	1-methyl-5-imidazolyl	
796(32)	2,5-diCl-C_6H_3	H	-S-CH_3	NH	1*H*-1-imidazolyl	
797(B29)	2,5-diCl-C_6H_3	H	-NH-CH_3	NH	1*H*-1-imidazolyl	HCl (1:2)

Table 20



Co.No. (Ex.No.)	R^4	n
774 (B17)	-CH_2-(4-Cl-C_6H_4)	3
775 (B17)	CH_3	3
776 (B17)	CH_3	4

Table 21 lists the experimental elemental analysis values for carbon, hydrogen and nitrogen of some of the compounds as prepared in the experimental part hereinabove.

Table 21

Comp No.	C	H	N
17	64.0	6.2	12.7
18	63.8	6.3	13.0
20	63.5	6.7	12.8
21	64.2	6.6	12.8
30	72.3	8.3	8.4
52	72.0	8.1	9.3
53	68.7	8.6	12.2
61	74.2	8.2	10.0

Comp No.	C	H	N
64	65.9	5.8	16.3
85	70.8	7.7	13.8
86	70.7	7.8	13.9
87	69.6	6.7	10.6
119	71.3	7.5	10.0
120	75.1	7.0	8.4
121	74.4	6.9	11.9
122	73.9	7.9	10.2

Comp No.	C	H	N
123	74.0	7.9	10.3
125	74.3	8.1	10.0
131	64.7	5.7	15.2
142	69.6	6.8	11.0
143	62.7	5.2	10.3
145	71.4	7.0	15.2
147	72.1	7.0	15.4
148	52.6	5.0	11.5

Comp No.	C	H	N
152	72.3	7.2	16.0
154	73.5	6.8	15.7
162	66.9	5.9	14.0
163	70.2	7.8	15.3
164	76.9	7.6	11.6
194	71.0	6.4	17.5
237	70.6	6.5	10.7
247	71.7	6.6	16.6
248	69.4	5.6	11.5
259	50.5	4.3	16.5
260	50.6	4.4	16.6
298	60.1	6.0	16.5
299	60.7	6.0	16.5
318	68.2	7.3	13.5
343	68.9	6.5	14.8
348	69.6	7.5	12.7
349	65.1	8.2	22.5
360	69.3	6.6	10.5
367	67.0	6.2	14.3
368	65.1	6.2	13.8
369	67.5	5.1	8.9
376	62.7	4.5	8.3
383	69.4	7.6	12.1
389	69.5	7.5	11.0
391	67.2	7.1	11.7
392	68.3	7.4	12.7
394	64.8	6.2	9.0
397	66.2	6.3	10.3
402	64.6	6.5	9.6
404	67.9	6.9	9.8
405	67.9	7.0	9.7
410	66.9	7.2	11.8
411	69.8	7.1	12.1
414	68.9	7.6	12.1
415	71.6	7.2	10.8

Comp No.	C	H	N
417	71.2	6.0	9.0
419	75.1	6.4	9.5
420	75.2	5.5	11.0
425	72.9	5.1	10.2
426	72.9	5.5	9.6
438	65.5	7.2	16.1
445	79.6	5.9	10.7
454	79.9	6.3	10.0
455	77.0	7.0	11.7
456	79.5	6.7	9.5
457	77.3	7.4	11.2
458	76.5	7.1	11.5
459	76.3	7.1	11.5
460	75.4	6.6	12.0
461	72.0	6.0	11.3
462	77.0	7.3	11.2
463	78.1	7.4	10.4
464	77.1	7.6	10.7
465	77.5	7.8	10.4
466	75.6	6.3	12.6
467	76.9	7.0	11.7
468	80.8	6.8	9.0
469	77.4	6.5	11.7
470	77.8	7.1	10.8
471	77.6	7.7	10.9
472	78.2	7.5	10.1
482	77.2	7.6	10.8
483	73.5	6.0	9.1
484	73.7	6.2	9.1
485	81.8	5.9	8.6
497	78.7	5.6	10.8
502	75.9	6.6	12.0
511	79.7	6.4	9.9
512	72.8	5.2	9.6
513	74.8	6.2	8.9

Comp No.	C	H	N
514	75.2	6.2	8.4
515	73.7	5.8	9.1
521	69.9	7.4	16.3
523	70.0	5.2	13.6
524	63.4	4.5	11.7
566	67.6	8.1	18.6
572	76.2	7.1	12.7
574	71.4	7.7	14.0
575	73.3	6.8	15.6
576	73.2	6.7	15.6
577	69.5	6.0	10.6
578	67.3	5.6	9.8
579	69.7	6.1	10.5
580	67.4	5.6	9.8
581	75.6	8.6	11.4
582	73.7	7.0	10.7
583	73.3	6.4	11.1
584	73.4	7.0	10.5
585	72.9	6.4	11.1
586	72.9	6.4	11.1
587	76.4	7.5	10.6
588	74.1	8.6	13.2
589	77.2	7.4	11.2
602	68.6	6.2	19.8
612	71.9	6.8	13.5
613	59.8	4.2	15.3
614	65.9	4.4	12.7
615	65.8	4.9	18.2
616	65.7	4.7	18.2
617	66.9	4.1	12.4
618	72.1	4.7	14.0
619	71.3	4.9	14.6
620	64.5	4.7	14.2
636	66.0	6.6	14.9
644	67.4	7.3	11.5

Comp No.	C	H	N
650	75.1	6.8	12.5
666	76.1	7.4	11.9
667	71.9	6.5	11.9
676	79.3	5.1	5.5
677	79.8	5.1	5.5
679	80.8	7.0	7.4
680	78.9	5.0	5.6
681	81.4	7.2	7.5
682	80.8	7.1	7.5
695	68.0	6.2	10.7

Comp No.	C	H	N
704	60.3	5.7	18.7
705	63.3	6.2	15.7
706	60.5	5.4	19.2
720	61.5	6.6	19.3
734	64.8	5.4	15.2
749	73.4	6.7	15.6
771	63.9	7.7	17.2
777	65.1	5.6	17.2
782	70.6	7.7	13.9
783	70.5	7.7	13.8

Comp No.	C	H	N
786	67.0	4.5	8.9
788	76.0	4.9	6.5
789	76.9	5.8	5.9
793	66.1	4.9	12.7
794	61.8	4.4	8.4
795	63.5	4.6	8.6
797	46.9	4.6	14.5

C. Pharmacological examples

Example C.1 : Inhibition of retinoic acid (RA) metabolism

MCF-7 human breast cancer cells were grown as stock cultures according to art-known protocols. One day before the experiment, RA is added to the stock cultures to stimulate RA-metabolism. At the start of the experiment, cell suspensions were incubated in a tissue culture medium containing ^{3}H-RA as the substrate. Different concentrations of the test compound (dissolved in 1% DMSO) were added to the incubation mixtures, and at the end of the incubation, the unmetabolized RA is separated from its polar metabolites. The fraction containing the polar ^{3}H-labelled metabolites was collected and counted in a scintillation counter. For each experiment, a control and a blank incubation were run in parallel. Table 22 list the IC_{50} value (defined as the concentration in M needed to reduce the amount of metabolites to 50 % of the control) .

Table 22

Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)
1	1.38E-10	13	3.57E-11	28	2.76E-09	38	1.04E-09	52	9.07E-10	67	3.34E-10
2	3.00E-11	17	9.99E-10	29	8.12E-09	39	1.04E-10	53	2.12E-09	68	1.72E-09
4	2.11E-09	18	8.72E-10	30	2.58E-08	41	1.98E-09	54	4.86E-09	69	2.50E-10
5	2.70E-10	21	2.89E-09	31	2.63E-09	45	1.72E-10	56	2.51E-11	70	2.95E-10
6	1.65E-09	22	1.04E-09	32	6.97E-10	46	1.95E-09	58	<1.00E-11	71	2.62E-10
7	7.90E-10	23	5.03E-10	33	1.01E-09	47	1.33E-09	61	7.34E-10	72	1.66E-09
8	9.37E-11	24	1.37E-09	34	1.03E-09	48	5.69E-10	63	6.70E-09	73	4.63E-10
10	1.55E-09	25	6.10E-08	35	2.24E-09	49	4.33E-10	64	6.60E-09	75	4.17E-10
11	2.63E-09	26	2.01E-10	36	1.43E-09	50	7.44E-09	65	3.79E-10	76	5.88E-10
12	3.65E-11	27	2.32E-10	37	1.00E-09	51	8.95E-10	66	3.56E-10	77	3.32E-10

Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)
78	2.27E-10	116	6.78E-10	156	3.10E-08	194	7.07E-09	232	1.51E-09	270	5.61E-09
79	3.42E-11	117	2.55E-10	157	8.48E-08	195	3.51E-08	233	2.43E-09	271	2.45E-09
80	4.83E-11	118	2.24E-09	158	>1.00E-07	196	2.23E-08	234	3.01E-09	272	4.81E-09
81	2.31E-10	119	9.40E-10	159	>1.00E-07	197	5.61E-09	235	6.94E-09	273	5.27E-08
82	1.16E-09	120	3.88E-09	160	8.65E-08	198	1.07E-08	236	9.84E-08	274	6.64E-09
83	1.62E-10	121	9.14E-10	161	1.87E-09	199	7.82E-09	237	1.82E-08	275	4.28E-09
84	1.74E-09	122	2.40E-09	162	2.88E-09	200	4.43E-08	238	>1.00E-07	276	1.60E-08
85	3.92E-09	123	2.47E-11	163	2.36E-09	201	3.58E-09	239	7.28E-10	277	1.17E-09
86	4.97E-10	124	3.97E-11	164	8.15E-09	202	1.84E-09	240	1.34E-09	288	1.28E-09
87	2.80E-10	125	1.94E-10	165	1.08E-08	203	2.28E-08	241	2.59E-09	289	5.07E-10
88	1.48E-10	126	<1.00E-11	166	1.75E-09	204	4.58E-09	242	2.82E-09	290	1.14E-09
89	1.31E-10	127	2.85E-11	167	4.16E-09	205	1.17E-08	243	3.59E-08	291	4.23E-09
90	2.36E-09	128	1.81E-11	168	2.36E-09	207	2.54E-08	244	2.30E-09	292	1.37E-10
91	9.35E-10	129	2.36E-11	169	5.31E-10	208	6.43E-09	245	2.79E-09	293	6.53E-09
92	2.21E-09	130	1.09E-11	170	1.22E-08	209	8.27E-09	246	2.10E-09	297	7.86E-10
93	1.59E-09	131	4.10E-09	171	8.58E-08	210	2.90E-08	247	3.55E-08	299	7.72E-10
94	1.06E-09	132	4.49E-09	172	3.41E-09	212	4.07E-09	248	1.79E-09	301	6.05E-09
95	1.48E-09	133	4.56E-09	173	5.17E-09	213	2.07E-09	249	7.58E-08	303	3.26E-09
96	1.09E-09	134	2.98E-09	174	1.60E-09	214	3.37E-09	250	1.49E-08	305	8.29E-11
97	1.32E-09	135	1.43E-09	175	4.83E-09	215	3.60E-08	251	3.93E-09	306	1.26E-09
98	1.64E-09	136	4.83E-09	176	1.87E-08	216	1.17E-08	252	2.59E-09	307	7.01E-10
99	5.77E-09	137	1.85E-09	179	3.69E-08	217	5.14E-09	253	5.55E-09	309	3.65E-09
102	6.78E-11	138	6.38E-09	180	5.69E-08	219	3.20E-09	254	6.47E-09	311	6.64E-10
103	7.11E-09	139	1.75E-09	181	1.41E-08	220	1.48E-09	255	6.24E-09	313	2.00E-11
104	4.07E-11	140	2.15E-08	182	1.31E-08	221	1.08E-09	256	3.20E-09	316	4.06E-09
105	5.16E-11	141	1.31E-09	183	7.40E-09	222	3.32E-09	259	9.29E-09	330	1.82E-09
106	1.69E-09	142	3.11E-08	184	5.15E-09	223	1.20E-09	260	2.43E-09	332	1.50E-09
107	1.44E-09	143	4.08E-09	185	3.97E-08	224	4.73E-09	261	2.22E-09	336	1.91E-09
108	2.34E-11	145	3.03E-09	186	>1.00E-07	225	8.28E-08	262	7.48E-09	339	1.23E-09
109	3.21E-10	147	3.30E-08	187	1.88E-08	226	1.69E-08	263	4.66E-09	346	2.04E-09
110	9.53E-10	148	1.86E-09	189	>1.00E-07	227	7.80E-09	264	2.71E-09	351	5.69E-09
111	1.03E-09	151	2.11E-09	190	>1.00E-07	228	7.30E-08	266	3.11E-08	352	2.57E-10
112	9.89E-10	152	5.18E-09	191	>1.00E-07	229	1.64E-09	267	7.75E-09	353	1.97E-09
113	8.52E-10	154	4.14E-09	192	3.34E-09	230	3.89E-09	268	7.79E-09	355	>1.00E-07
115	8.17E-09	155	5.01E-08	193	1.21E-08	231	1.86E-09	269	2.66E-09	356	>1.00E-07

Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)
357	>1.00E-07	426	>1.00E-07	484	3.43E-09	587	3.16E-08	639	1.68E-09	690	>1.00E-07
358	>1.00E-07	427	8.34E-09	485	>1.00E-07	588	4.88E-08	640	2.17E-09	691	>1.00E-07
359	6.25E-09	432	8.10E-10	486	2.77E-08	589	2.75E-09	642	1.16E-09	692	3.80E-08
360	1.08E-09	435	2.80E-09	488	>1.00E-07	590	2.78E-09	644	2.96E-10	693	>1.00E-07
361	>1.00E-07	445	1.92E-07	489	>1.00E-07	591	4.01E-08	645	8.02E-09	695	>1.00E-07
362	1.43E-08	454	5.25E-08	490	>1.00E-07	592	4.15E-09	646	3.07E-09	696	8.07E-09
363	1.42E-09	455	2.87E-09	491	1.84E-09	593	2.70E-09	649	7.32E-09	697	1.71E-08
364	1.41E-09	456	1.40E-07	492	4.07E-09	594	4.81E-09	650	4.86E-09	698	3.96E-08
365	1.08E-09	457	2.50E-08	493	8.77E-09	595	3.83E-09	651	1.05E-08	699	9.69E-09
366	3.05E-09	458	3.22E-09	497	3.76E-08	596	7.92E-09	652	>1.00E-07	700	1.20E-08
367	1.25E-09	459	1.77E-08	502	3.29E-08	597	5.00E-09	653	1.34E-09	707	1.30E-08
368	5.83E-10	460	3.63E-08	511	1.05E-08	598	2.39E-08	654	2.34E-09	708	1.61E-09
369	8.22E-08	461	1.69E-08	512	6.16E-07	599	6.36E-09	655	1.61E-08	709	2.40E-09
370	8.34E-08	462	>1.00E-06	513	8.60E-07	600	3.67E-08	656	1.47E-09	710	1.88E-10
371	3.59E-09	463	2.45E-08	514	>1.00E-06	601	2.00E-08	657	5.36E-09	711	>1.00E-07
372	1.97E-09	464	1.49E-07	515	>1.00E-06	602	2.57E-08	658	5.48E-09	712	4.30E-12
376	<1.00E-10	465	5.04E-08	516	>1.00E-06	603	>1.00E-07	659	>1.00E-07	713	1.38E-09
378	1.74E-09	466	>1.00E-06	517	3.69E-08	604	2.89E-09	660	6.37E-09	715	1.54E-10
383	7.29E-10	467	2.58E-09	518	>1.00E-07	605	1.40E-08	661	3.40E-08	718	1.33E-10
385	6.75E-09	468	>1.00E-07	519	3.80E-09	606	1.36E-08	662	3.58E-10	722	4.14E-09
388	8.29E-10	469	>1.00E-07	524	>1.00E-06	608	6.61E-09	663	1.95E-09	723	1.13E-09
389	5.67E-11	470	1.87E-08	558	1.32E-09	609	1.09E-08	664	1.56E-09	724	1.18E-09
393	9.55E-10	471	>1.00E-07	574	1.78E-09	610	6.53E-09	665	5.91E-09	725	3.29E-09
404	1.35E-09	472	9.51E-08	575	2.57E-08	611	3.42E-09	666	1.45E-08	726	3.71E-09
405	3.68E-09	473	>1.00E-07	576	2.01E-08	612	1.68E-08	667	1.57E-09	727	1.64E-09
412	3.99E-09	474	1.59E-08	577	4.23E-08	613	1.80E-06	668	3.16E-09	728	1.41E-09
413	5.27E-09	475	>1.00E-07	578	7.67E-09	614	2.78E-07	669	8.66E-09	729	>1.00E-07
415	2.64E-09	476	3.55E-08	579	1.24E-08	615	>1.00E-06	670	5.72E-09	730	1.59E-08
416	3.67E-10	477	>1.00E-06	580	3.13E-08	616	>1.00E-06	679	>1.00E-06	731	>1.00E-07
420	8.38E-08	478	1.63E-09	581	>1.00E-07	617	1.51E-07	680	1.21E-08	732	1.93E-08
421	>1.00E-07	479	>1.00E-07	582	1.58E-09	618	1.57E-08	681	>1.00E-06	733	2.41E-09
422	>1.00E-08	480	4.25E-09	583	2.78E-09	619	3.57E-08	682	>1.00E-07	734	2.25E-09
423	4.08E-08	481	2.83E-09	584	6.51E-09	620	>1.00E-06	685	9.08E-08	735	>1.00E-07
424	>1.00E-07	482	1.95E-09	585	7.21E-09	621	1.25E-09	686	4.31E-08	736	7.45E-09
425	3.81E-08	483	1.98E-08	586	3.74E-09	623	1.38E-09	687	>1.00E-07	737	2.36E-09

Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)	Co. No.	IC_{50} (in M)
738	2.03E-09	743	1.10E-08	751	6.70E-08	762	4.08E-08	774	5.27E-09	782	1.26E-09
739	4.21E-08	744	>1.00E-07	753	>1.00E-07	763	5.62E-09	776	4.39E-09	783	3.98E-08
740	1.29E-09	745	3.87E-09	755	4.35E-09	764	2.33E-08	778	7.59E-08		
741	1.44E-09	746	>1.00E-07	758	1.88E-09	772	1.46E-10	780	4.57E-09		
742	2.61E-10	749	1.26E-07	761	>1.00E-07	773	>1.00E-07	781	3.24E-09		

Example C.2 : "Vaginal Keratinization Test on Ovariectomized Rats"

Ovariectomized rats were injected subcutaneously with a sesame oil solution containing 100 µg of estradiol undecylate in a volume of 0.1 ml per 100 g body weight and control animals were injected with sesame oil. On day one, two and three, test animals were treated once daily with a *per os* dose of the test compound and control animals with the drug vehicle (PEG 200). One day after the last treatment, the animals were sacrificed and their vaginas were processed for histological evaluation according to the method described in J. Pharmacol. Exp. Ther. *261(2)*, 773-779 (1992). A dose at which 50 % of the tested rats show complete suppression of the estradiol undecylate induced keratinization effects is defined as an active dose. Table 23 lists the lowest active dose (LAD in mg/kg)of the compounds of formula (I) which were tested.

Table 23

Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)
2	5.00	24	2.50	41	2.50	61	2.50	77	2.50	93	2.50
3	>2.50	25	10.00	43	2.50	62	>5.00	78	1.25	94	5.00
4	0.60	26	5.00	44	2.50	63	>5.00	79	2.50	95	5.00
5	>2.50	27	5.00	45	2.50	64	>5.00	80	>2.50	96	2.50
6	2.50	28	2.50	46	>2.50	65	5.00	81	2.50	97	2.50
7	>2.50	29	5.00	47	2.50	66	2.50	82	2.50	98	5.00
8	>2.50	30	>5.00	48	2.50	67	2.50	83	>2.50	99	2.50
10	2.50	31	5.00	49	2.50	68	5.00	84	>2.50	102	5.00
11	>2.50	32	5.00	50	2.50	69	2.50	85	2.50	103	>2.50
13	>2.50	33	5.00	52	2.50	70	5.00	86	2.50	104	2.50
15	>2.50	34	2.50	53	>2.50	71	>5.00	87	1.25	105	2.50
18	2.50	35	2.50	55	>2.50	72	2.50	88	2.50	106	2.50
20	2.50	36	5.00	56	>5.00	73	>2.50	89	2.50	107	>2.50
21	5.00	37	5.00	57	>5.00	74	2.50	90	2.50	109	2.50
22	2.50	38	5.00	58	5.00	75	2.50	91	2.50	110	>2.50
23	2.50	39	0.60	59	>2.50	76	>2.50	92	5.00	111	>2.50

Co. No.	LAD (mg/kg)
112	2.50
113	>2.50
114	2.50
115	>2.50
116	2.50
117	>2.50
118	2.50
121	>2.50
122	>2.50
123	2.50
125	2.50
126	2.50
127	>2.50
128	5.00
129	2.50
130	5.00
131	5.00
132	5.00
133	>5.00
134	5.00
135	2.50
136	5.00
137	>5.00
138	>5.00
139	10.00
140	5.00
141	>10.00
142	5.00
143	10.00
148	>5.00
151	5.00
152	>5.00
154	5.00
155	>10.00
156	>10.00

Co. No.	LAD (mg/kg)
157	>10.00
158	>10.00
159	>10.00
160	10.00
161	>2.50
162	>5.00
163	20.00
164	20.00
165	>20.00
166	5.00
167	10.00
168	10.00
169	10.00
170	10.00
171	>10.00
172	10.00
173	10.00
174	10.00
175	10.00
176	>10.00
178	>10.00
179	>10.00
180	>10.00
181	10.00
182	10.00
183	>10.00
184	>10.00
185	10.00
186	>10.00
187	>10.00
189	>10.00
190	>10.00
191	>10.00
192	>10.00
193	>10.00

Co. No.	LAD (mg/kg)
194	10.00
195	>10.00
196	>10.00
197	>10.00
198	>10.00
199	>10.00
200	>10.00
201	>10.00
202	>10.00
203	>10.00
204	>10.00
205	>10.00
207	10.00
208	>10.00
209	5.00
210	20.00
212	20.00
213	20.00
214	20.00
215	20.00
216	20.00
217	10.00
219	20.00
220	20.00
221	10.00
222	20.00
223	5.00
224	>10.00
227	>10.00
228	>10.00
229	>10.00
230	>10.00
231	>10.00
232	>10.00
233	>10.00

Co. No.	LAD (mg/kg)
234	10.00
235	5.00
236	5.00
237	5.00
238	5.00
239	10.00
240	10.00
241	10.00
242	>10.00
243	10.00
244	10.00
245	10.00
246	10.00
247	10.00
248	2.50
249	5.00
250	>10.00
251	10.00
252	>10.00
253	>5.00
254	>5.00
255	5.00
256	>2.50
261	>10.00
262	20.00
263	>10.00
264	>10.00
266	>10.00
267	>10.00
268	>10.00
269	>10.00
270	>10.00
271	10.00
272	>10.00
273	>10.00

Co. No.	LAD (mg/kg)
274	>10.00
275	>10.00
276	>10.00
277	>5.00
278	2.50
279	2.50
280	>2.50
281	>2.50
283	2.50
284	2.50
285	>2.50
286	>2.50
287	>2.50
288	>2.50
289	>2.50
290	2.50
291	>2.50
292	>2.50
293	>2.50
294	>2.50
295	>2.50
297	>2.50
300	>2.50
301	>2.50
302	>2.50
304	>2.50
306	>2.50
307	>2.50
308	>2.50
309	>2.50
310	2.50
311	2.50
312	>2.50
313	2.50
314	>2.50

Co. No.	LAD (mg/kg)
315	>2.50
316	5.00
317	>5.00
318	>2.50
319	>5.00
320	5.00
322	>2.50
324	>2.50
325	2.50
326	>2.50
327	>2.50
328	>2.50
329	>2.50
330	2.50
332	>2.50
333	>2.50
337	2.50
338	>2.50
339	>2.50
340	2.50
341	>2.50
342	>2.50
343	>2.50
346	>5.00
347	>5.00
348	>2.50
349	>2.50
350	>2.50
351	>5.00
352	>5.00
353	>5.00
354	>5.00
355	>10.00
356	>10.00
357	>10.00

Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)	Co. No.	LAD (mg/kg)
358	>10.00	397	>2.50	436	>5.00	484	>5.00	576	10.00	612	10.00
359	>10.00	398	>5.00	437	>2.50	485	5.00	577	10.00	613	>20.00
360	2.50	400	>2.50	438	>2.50	486	5.00	578	>10.00	614	>20.00
361	10.00	401	>2.50	439	>2.50	487	>5.00	579	10.00	615	>20.00
362	10.00	402	>5.00	445	>20.00	489	2.50	580	10.00	618	>20.00
363	>10.00	403	>5.00	454	>20.00	490	2.50	581	20.00	619	>20.00
364	2.50	404	5.00	455	2.50	492	>2.50	582	>10.00	621	1.25
365	10.00	405	5.00	456	>20.00	493	>2.50	583	10.00	623	>5.00
366	>10.00	406	>5.00	457	>20.00	494	>2.50	584	10.00	624	>2.50
367	2.50	407	>5.00	458	5.00	495	>2.50	585	10.00	626	2.50
368	2.50	408	>5.00	459	20.00	497	>20.00	586	>10.00	627	>2.50
369	10.00	409	5.00	460	>20.00	502	5.00	587	>10.00	628	>2.50
370	>10.00	410	>5.00	461	10.00	511	>20.00	588	10.00	629	>2.50
371	10.00	411	2.50	462	20.00	512	>20.00	589	10.00	630	>2.50
372	5.00	412	>2.50	463	20.00	513	>20.00	590	>10.00	631	>2.50
374	2.50	413	5.00	464	>20.00	514	>20.00	591	>10.00	632	>2.50
375	>5.00	414	5.00	465	>20.00	515	>20.00	592	>10.00	636	2.50
376	2.50	416	>5.00	466	>20.00	518	>10.00	593	>10.00	638	>2.50
378	2.50	417	>5.00	467	>20.00	519	>10.00	594	>10.00	639	2.50
379	>2.50	419	>5.00	468	10.00	521	10.00	595	10.00	640	>2.50
380	>2.50	420	>20.00	469	>10.00	524	20.00	596	10.00	642	2.50
381	>2.50	421	>10.00	470	>20.00	532	>10.00	597	>10.00	644	2.50
383	>2.50	422	>10.00	471	>10.00	551	>2.50	598	>10.00	645	>5.00
384	>2.50	423	20.00	472	>20.00	552	>2.50	599	>20.00	646	5.00
385	>2.50	424	>10.00	473	>10.00	554	2.50	600	>10.00	647	>5.00
386	>2.50	425	>10.00	474	>10.00	555	>2.50	601	10.00	649	5.00
387	>2.50	426	>10.00	475	>10.00	557	>5.00	602	>10.00	650	10.00
389	>2.50	427	2.50	476	>10.00	558	>5.00	603	>10.00	651	5.00
390	>2.50	428	>2.50	477	>10.00	560	>5.00	604	>10.00	652	10.00
391	>5.00	429	>2.50	478	2.50	562	5.00	605	>10.00	653	5.00
392	>5.00	431	>2.50	479	>10.00	566	5.00	606	>10.00	654	5.00
393	5.00	432	>2.50	480	10.00	570	>5.00	608	>10.00	655	>10.00
394	>2.50	433	>2.50	481	10.00	572	>5.00	609	10.00	656	10.00
395	>5.00	434	>2.50	482	10.00	574	20.00	610	>10.00	657	>10.00
396	>2.50	435	>2.50	483	>5.00	575	20.00	611	10.00	658	>10.00

Co. No.	LAD (mg/kg)
659	>10.00
660	>10.00
661	>10.00
662	5.00
663	2.50
664	5.00
665	2.50
666	2.50
667	5.00
668	5.00
669	5.00
670	>2.50
679	>20.00
680	>20.00

Co. No.	LAD (mg/kg)
681	>20.00
682	>20.00
686	>10.00
690	>10.00
692	>10.00
695	>10.00
696	>10.00
697	10.00
698	20.00
700	5.00
704	>5.00
705	>5.00
706	5.00
707	5.00

Co. No.	LAD (mg/kg)
708	>5.00
709	5.00
710	2.50
711	5.00
712	5.00
713	2.50
714	2.50
715	>2.50
716	>2.50
717	>2.50
718	2.50
720	>2.50
721	>2.50
722	5.00

Co. No.	LAD (mg/kg)
723	5.00
724	2.50
725	5.00
726	5.00
727	>10.00
728	5.00
729	2.50
730	>10.00
732	>10.00
733	>10.00
734	10.00
735	10.00
736	>10.00
737	>10.00

Co. No.	LAD (mg/kg)
738	10.00
739	>10.00
740	20.00
741	10.00
742	10.00
743	>10.00
745	>5.00
746	>5.00
749	>20.00
751	10.00
753	>10.00
754	10.00
758	>5.00
761	>5.00

Co. No.	LAD (mg/kg)
762	>5.00
763	>5.00
764	>5.00
766	>2.50
768	>2.50
772	>5.00
773	>10.00
774	10.00
776	>20.00
778	5.00
782	2.50
783	5.00
784	>5.00
785	5.00

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention. "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

Example D.1 : oral solution

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxy-benzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propane-triol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of A.I. per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example D.2 : oral drops

500 g of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were

added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I. The resulting solution was filled into suitable containers.

Example D.3 : capsules

20 g of A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of A.I.

Example D.4 : injectable solution

0.5 mg A.I. 1, 50 mg glucose anhydrous and 0.332 ml concentrated hydrochloric acid were mixed with 0.8 ml water for injections. Sodium hydroxide was added until pH = 3.2 ± 0.1 and water was added to 1 ml. The solution was sterilized and filled in sterile containers.

Example D.5 : film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinyl-pyrrolidone (Kollidon-K 90 ®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel ®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG ®) in 75 ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated color suspension (Opaspray K-1-2109 ®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example D.6 : 2% cream

75 mg stearyl alcohol, 2 mg cetyl alcohol, 20 mg sorbitan monostearate and 10 mg isopropyl myristate are introduced into a doublewall jacketed vessel and heated until

the mixture has completely molten. This mixture is added to a separately prepared mixture of purified water, 200 mg propylene glycol and 15 mg polysorbate 60 having a temperature of 70 to 75°C while using a homogenizer for liquids. The resulting emulsion is allowed to cool to below 25°C while continuously mixing. A solution of 20 mg A.I., 1 mg polysorbate 80 and purified water and a solution of 2 mg sodium sulfite anhydrous in purified water are next added to the emulsion while continuously mixing. The cream, 1 g of the A.I. is homogenized and filled into suitable tubes.

Example D.7 : 2% topical gel

To a solution of 200 mg hydroxypropyl β-cyclodextrine in purified water is added 20 mg of A.I. while stirring. Hydrochloric acid is added until complete dissolution and then sodium hydroxide is added until pH 6.0. This solution is added to a dispersion of 10 mg carrageenan PJ in 50 mg propylene glycol while mixing. While mixing slowly, the mixture is heated to 50°C and allowed to cool to about 35°C whereupon 50 mg ethyl alcohol 95% (v/v) is added. The rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Example D.8 : 2% topical cream

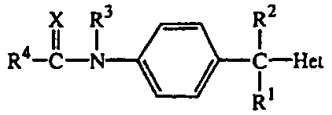
To a solution of 200 mg hydroxypropyl β-cyclodextrine in purified water is added 20 mg of A.I. while stirring. Hydrochloric acid is added until complete dissolution and next sodium hydroxide is added until pH 6.0. While stirring, 50 mg glycerol and 35 mg polysorbate 60 are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of 100 mg mineral oil, 20 mg stearyl alcohol, 20 mg cetyl alcohol, 20 mg glycerol monostearate and 15 mg sorbate 60 having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Example D.9 : 2% liposome formulation

A mixture of 2 g A.I. microfine, 20 g phosphatidyl choline, 5 g cholesterol and 10 g ethyl alcohol is stirred and heated at 55-60°C until complete dissolution and is added to a solution of 0.2 g methyl paraben, 0.02 g propyl paraben, 0.15 g disodium edetate and 0.3 g sodium chloride in purified water while homogenizing. 0.15 g Hydroxypropyl-methylcellulose in purified water ad 100 g is added and the mixing is continued until swelling is complete.

Claims

1. A compound having the formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

X represents -O-, -S- or -NR^3-;

R^1 represents hydrogen, hydroxy, C_{1-6}alkyl or aryl;

R^2 represents hydrogen; C_{1-12}alkyl; C_{3-7}cycloalkyl; C_{2-8}alkenyl; aryl; Het^1; or C_{1-12}alkyl substituted with one or two substituents selected from C_{3-7}cycloalkyl, hydroxy, C_{1-4}alkyloxy, cyano, amino, mono- and di(C_{1-4}alkyl)amino, mono- or di(arylC_{1-4}alkyl)amino, di(arylC_{1-4}alkyl)aminocarbonyloxy, (C_{1-4}alkyl)(arylC_{1-4}alkyl)amino, mono- and di(aryl)amino, (C_{1-4}alkyl)(di(C_{1-4}alkyl)-aminoC_{1-4}alkyl)amino, pyrrolidinyl , piperidinyl, piperazinyl optionally substituted with C_{1-4}alkyl, morpholinyl, perhydro-azepinyl, carboxyl, C_{1-4}alkyl-oxycarbonyl, aminocarbonyl, mono- and di(C_{1-4}alkyl)aminocarbonyl, aryl, aryloxy and arylthio; or

R^1 and R^2 taken together may form a bivalent radical of formula -R^1-R^2- wherein -R^1-R^2- represents -$(CH_2)_n$- wherein n is 2, 3, 4, 5 or 6;

R^3 represents hydrogen, C_{1-6}alkyl, aryl, Het^1 or C_{1-6}alkyl substituted with aryl or Het^1;

R^4 represents hydrogen; hydroxy; mercapto; C_{1-6}alkyloxy; C_{1-6}alkylthio; aryloxy; arylthio; Het^1-oxy; Het^1-thio; C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-oxy, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonylC_{1-6}alkyl, carboxyl, C_{1-6}alkyloxy-carbonyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, aryl, Het^1; C_{2-8}alkenyl optionally substituted with one, two or three substituents selected from halo, C_{3-7}cycloalkyl, aryl, Het^1; C_{2-8}alkynyl optionally substituted with halo, C_{3-7}cycloalkyl, aryl; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl or aryl; C_{5-7}cycloalkenyl optionally substituted with C_{1-6}alkyl or aryl; aryl; Het^1; or

-Alk-NR^3R^5 (i) or

-NR^3R^5 (ii)

wherein Alk represents C_{1-6}alkanediyl; and

R^5 represents hydrogen, C_{1-6}alkyl, aryl, Het^1, (aryl or Het^1)C_{1-6}alkyl, (aryl or Het^1)carbonyl or (aryl or Het^1)C_{1-6}alkyloxycarbonyl;

aryl represents indanyl, indenyl, naphtyl, 5,6,7,8-tetrahydro-2-naphtalenyl, phenyl; said indanyl, indenyl, naphtyl or phenyl may be substituted with one, two, three, four or five substituents each independently selected from hydroxy, halo, nitro, cyano, amino, azido, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, phenyl, phenyloxy, phenylC_{1-6}alkyloxy, pyridinylC_{1-6}alkyloxy, C_{1-6}alkyloxy, formyl, carboxyl and C_{1-6}alkylcarbonyl; or two adjacent carbon atoms on said phenyl may be substituted by a single bivalent radical having the formula C_{1-12}alkanediyl or polyhaloC_{1-12}alkanediyl;

Het represents an unsaturated heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl and pyridinyl; each of said unsaturated heterocycles may optionally be substituted with amino, mercapto, C_{1-6}alkyl, C_{1-6}alkylthio or aryl; and

Het^1 represents a monocyclic heterocycle selected from pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,3,4-triazolyl, 1,2,4-triazolyl, tetrahydrofuranyl, furanyl, thiolanyl, thienyl, dioxolanyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, tetrahydropyranyl, pyranyl, morpholinyl and dioxanyl; each of said monocyclic heterocycles may be optionally substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl; or a bicyclic heterocycle selected from indolinyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, benzothienyl, 2*H*-1-benzopyranyl, 3,4-dihydro-2*H*-1-benzopyranyl, benzthiazolyl, isoquinolinyl, quinolinyl, 3,4-dihydroquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, chromanyl, 1,4-benzodioxinyl, 1,4-benzoxathianyl, benzodioxanyl and benzodioxolanyl; each of said bicyclic heterocycles may be substituted with one or two substituents each independently selected from C_{1-4}alkyl, hydroxy, amino, halo, aryl, arylcarbonyl or C_{1-4}alkyloxycarbonyl.

2. A compound as claimed in claim 1 wherein R^1 represents hydrogen, hydroxy or C_{1-6}alkyl; and R^2 represents hydrogen; C_{1-12}alkyl; C_{3-7}cycloalkyl; C_{2-8}alkenyl; aryl; Het^1; or C_{1-12}alkyl substituted with one or two substituents selected from hydroxy, C_{1-4}alkyloxy, cyano, mono- and di(C_{1-4}alkyl)amino, mono- or di(arylC_{1-4}alkyl)amino, di(arylC_{1-4}alkyl)aminocarbonyloxy, (C_{1-4}alkyl)(arylC_{1-4}alkyl)amino, (C_{1-4}alkyl)(di(C_{1-4}alkyl)aminoC_{1-4}alkyl)amino, piperidinyl, piperazinyl optionally substituted with C_{1-4}alkyl, morpholinyl, C_{1-4}alkyloxycarbonyl, aryl, aryloxy and arylthio; or R^1 and R^2 taken together may

form a bivalent radical of formula $-R^1-R^2-$ wherein $-R^1-R^2-$ represents $-(CH_2)_n-$ wherein n is 2.

3. A compound according to claim 1 or 2 wherein R^3 is hydrogen; X is O and R^4 is aryl or C_{1-12}alkyl optionally substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, aryloxy, arylthio, Het^1-thio, C_{3-7}cycloalkyl optionally substituted with hydroxycarbonyl-C_{1-6}alkyl, carboxyl, C_{1-6}alkyloxycarbonyl, arylC_{1-6}alkylthio, aryl, Het^1; or a radical of formula (ii).

4. A compound according to claim 1 or 2 wherein R^3 is hydrogen, X is S and R^4 is a radical of formula (ii).

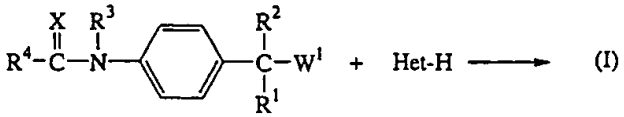
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of the claims 1 to 4.

6. A process of preparing a pharmaceutical composition as claimed in claim 5, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4.

7. A compound as claimed in any one of claims 1 to 4 for use as a medicine.

8. Use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for treating oncology disorders and keratinization disorders.

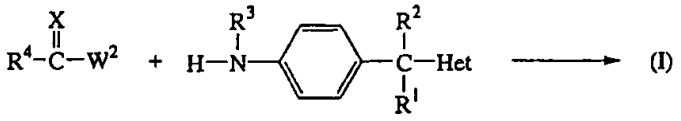
9. A process of preparing a compound as claimed in claim 1, characterized by
a) reacting an intermediate of formula (II) wherein W^1 is an appropriate leaving group with an intermediate of formula (III) or a functional derivative thereof in a reaction-inert solvent and in the presence of a suitable base;



(II) (III)

and in case W^1 is an hydroxy group, in the presence of triphenylphosphine and diethyl azodicarboxylate or a functional derivative of any of said reagents, or in the presence of 1-hydroxy-1*H*-benzotriazole and dicyclohexylcarbodiimide;

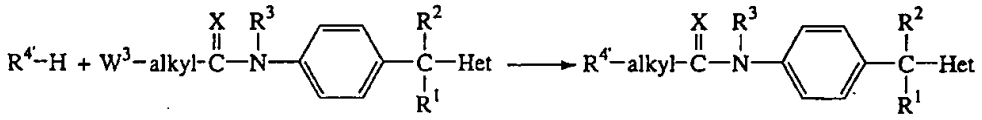
b) *N*-alkylation of an intermediate of formula (IV) with an intermediate of formula (V) wherein W^2 is an appropriate leaving group in a reaction-inert solvent and optionally in the presence of a suitable base; or



(V) (IV) (I)

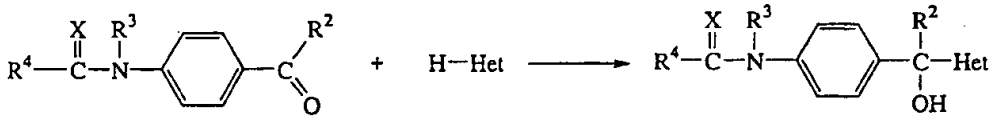
N-alkylation of an intermediate of formula (IV) with an anhydride, a cyanate, a thiocyanate, an isocyanate or an isothiocyanate optionally in the presence of an acid;

c) reacting an intermediate of formula (VI) wherein W^3 is a suitable leaving group with an intermediate of formula $R^{4'}$-H (VII) wherein $R^{4'}$ is a Het^1C_{1-12}alkyl or a radical of formula (i) in a reaction-inert solvent in the presence of an appropriate base; thus forming compounds of formula (I-a);



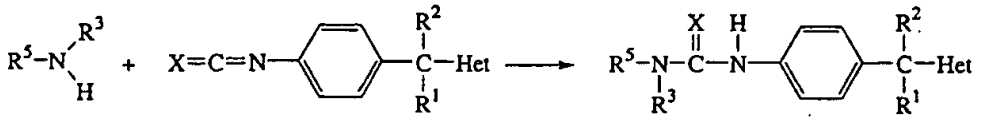
(VII) (VI) (I-a)

d) reacting an intermediate of formula (VIII) with Het-H (III) or a functional derivative thereof, in the presence of *n*-butyllithium or a functional derivative in a reaction-inert solvent and optionally in the presence of chlorotriethylsilane; thus obtaining compounds of formula (I) wherein R^1 is hydroxy, said compounds being represented by formula (I-b);



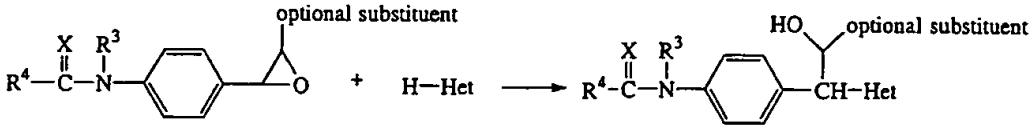
(VIII) (III) (I-b)

e) reacting a primary or secundary amine of formula (VIII) with an intermediate of formula (IX) in a reaction-inert solvent; thus obtaining compounds of formula (I) wherein R^3 is hydrogen and R^4 is attached by a nitrogen atom to the remainder of the molecule, said compounds being represented by formula (I—c);



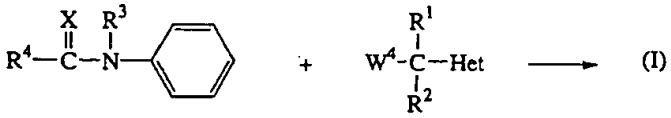
(IX) (X) (I-c)

f) reacting an intermediate of formula (XI) with Het-H (XII) or a functional derivative thereof, in a reaction-inert solvent; thus obtaining compounds of formula (I) wherein R^2 is optionally substituted hydroxymethyl, being represented by formula (I-d);



(XI) (XII) (I-d)

g) reacting an intermediate of formula (XIII) wherein W^4 is a suitable leaving group with an intermediate of formula (XIV) in an appropriate solvent and in the presence of an acid;



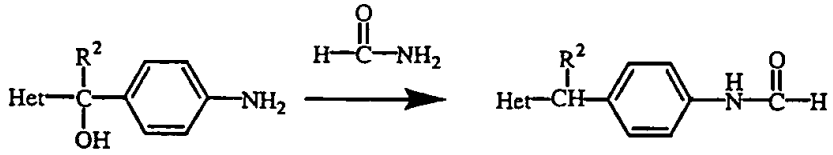
(XIV) (XIII)

h) reacting an intermediate corresponding to a compound of formula (I) wherein R^2 is LG-C_{1-12}alkyl wherein LG is an appropriate leaving group, with C_{1-4}alkylO^-M^+ wherein M^+ is a suitable metal ion in a suitable solvent; thus obtaining compounds of formula (I) wherein R^2 is C_{1-4}alkyloxyC_{1-12}alkyl;

i) reducing an intermediate of formula (XV) wherein $R^{2'}$ is the same as R^2 being an optionally substituted C_{1-12}alkyl, using a suitable reducing agent in a suitable solvent; thus obtaining a compound of formula (I-e);

(XV) (I-e)

j) reacting an intermediate of formula (XXIII) with formamide in the presence of an acid; thus forming a compound of formula (I-f);



(XXIII) (I-f)

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of

formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) an effective amount of retinoic acid, a derivative thereof or a stereochemically isomeric form thereof, and (b) an effective amount of a compound of formula (I) as described in any one of claims 1 to 4.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) an effective amount of calcitriol or a prodrug thereof, and (b) an effective amount of a compound of formula (I) as described in any one of claims 1 to 4.

12. A product containing (a) a pharmaceutical composition containing an effective amount of retinoic acid, a derivative thereof or a stereochemically isomeric form thereof and a pharmaceutical acceptable carrier,, and (b) a pharmaceutical composition containing an effective amount of a compound of formula (I) as described in any one of claims 1 to 4, and a pharmaceutical acceptable carrier, as a combined preparation for simultaneous, separate or sequential use in dermatological or oncological disorders.

13. A product containing (a) a pharmaceutical composition containing an effective amount of calcitriol or a prodrug thereof and a pharmaceutical acceptable carrier, and (b) a pharmaceutical composition containing an effective amount of a compound of formula (I) as described in any one of claims 1 to 4, and a pharmaceutical acceptable carrier, as a combined preparation for simultaneous, separate or sequential use in dermatological or oncological disorders.

14. A product containing a) a pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to any of claims 1 to 4 and a pharmaceutically acceptable carrier; and b) a pharmaceutical composition comprising a pharmaceutically effective amount of an anti-neoplastic agent and a pharmaceutically acceptable carrier, as a combined preparation for simultaneous, separate or sequential use in dermatological or oncological disorders.

INTERNATIONAL SEARCH REPORT

Int. donal Application No
PCT/EP 98/08126

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/56 C07D249/08 C07D213/40 C07D401/12 C07D403/12
C07D405/12 C07D409/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 371 564 A (JANSSEN PHARMACEUTICA N. V.) 6 June 1990 see page 39, table 3-a ---	1-3
X	WO 97 16443 A (JANSSEN PHARMACEUTICA N. V.) 9 May 1997 see page 7, formula (VI); page 13, formula (VI); page 19, example 1, especially lines 21 and 22 ---	1-3
A	EP 0 371 559 A (JANSSEN PHARMACEUTICA N. V.) 6 June 1990 cited in the application see claims 1,10-12,17,18 --- -/--	1,5,7,8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	27/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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